9/18/88

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

SEP 18 1988

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MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Danitol™ (fenpropathrin) - Data Review and Registration.

EPA Nos. 39398-RA, 39398-RT
Record Nos. 183403, 183405

Project No. 7-0148
Tox. Chem. No. 273d

TO: George LaRocca (PM Team #15)
Registration Division (TS-767c)

FROM: John E. Whalan, D.A.B.T., Toxicologist
Section I, Insecticide, Rodenticide Branch
Health Effects Division (TS-769c)

John E Whalan 9-2-88

THRU: Edwin R. Budd, Section Head
Section I, Insecticide, Rodenticide Branch
Health Effects Division (TS-769)

9/14/88

9/18/88

The Applicant, Sumitomo Chemical America, Inc., has requested registration of Danitol technical (fenpropathrin, alpha-Cyano-3-phenoxybenzyl-2,2,3,3-tetramethyl-1-cyclopropanecarboxylate) and Danitol™ 2.4 EC Spray for use on ornamentals and nonbearing fruit trees to control insects and mites. The following studies were submitted in support of the requested registrations:

TECHNICAL:

81-3 The Acute Vapor Inhalation Toxicity of Danitol Technical (SX-1713) in Mice and Rats
83-1,2 S-3206 Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats
83-1,2 S-3206 Two-Year Feeding Study in Mice (terminated after 13 weeks of treatment)
83-1,2 S-3206 Two-Year Feeding Study in Mice
83-3 The Effects of S-3206 on Pregnancy of the New Zealand White Rabbit
83-4 Effect of S-3206 on Multiple Generations of the Rat
84-2 Gene Mutation Test of S-3206 in Bacterial System.
84-2 Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells In Vitro Test Substance: S-3206.
84-2 Micronucleus Test of S-3206.
84-2 In Vitro Sister Chromatid Exchange Test of S-3206 in CHO-kl Cells.
85-3 The Percutaneous Absorption of Fenpropathrin Technical (SX-1491) in Adult Male Rats

DANITOL 2.4 EC:

81-3 The Acute Inhalation Toxicity of Danitol 2.4 EC (SX-1714) in Rats
81-3 The Acute Inhalation Toxicity of Danitol 2.4 EC (SX-1714) in Mice

The technical product (90% active ingredient) is used for formulation only. Danitol 2.4 EC Spray (30% active ingredient; 2.4 lbs a.i./gallon) will be diluted (1-2 teaspoons per 3 gallons of water), and will be sprayed with ground equipment. It will not be used on food crops.

The Applicant's intention was to register Danitol 2.4 EC Spray for homeowner use. As mentioned in a previous memorandum (John Whalan; EPA No. 39398-RT; October 30, 1987), Danitol 2.4 EC Spray is probably too toxic for domestic use by homeowners because it is a Toxicity Category II product (based on acute oral toxicity and eye irritation). Toxicology Branch believes that the acute oral toxicity of this product (oral LD_{50} = 72.1 mg/kg) warrants classification of this product for Restricted Use only (ref. 40 CFR §162.11). Since a Restricted Use classification is inconsistent with the applicant's request for homeowner use, this memorandum will consider only non-domestic use.

DATA SUPPORTING REGISTRATION:

The data available to support the registration of the technical product are listed in the 8-Point Summary (attached). The only database deficiency is an acute inhalation LC_{50} study using the technical product. This requirement may be waived if RD can confirm that the technical product (a solid) cannot be milled to produce an inhalable aerosol. The data available to support the registration of Danitol 2.4 EC are as follows:

	End-Use Product (Danitol 2.4 EC)	Acceptable Data
81-1	Oral LD_{50}	Yes
81-2	Dermal LD_{50}	Yes
81-3	Inhalation LC_{50}	Yes
81-4	Primary eye irritation	Yes
81-5	Primary dermal irritation	Yes
81-6	Dermal sensitization	Yes
82-2	21-Day dermal	Yes

The Toxicity Categories for Danitol technical are I for oral toxicity, II for dermal toxicity, III for primary eye irritation, and IV for primary dermal irritation. The technical is not a dermal sensitizer in guinea pigs. Considering this toxicity profile, the following label changes are suggested:

1. The Signal Word should be changed to "DANGER" to reflect the acute oral hazard. In addition, the word "POISON" (in red) together with the skull and crossbones must appear in close proximity to the signal word.

2. The Precautionary Statements should be modified as follows:

   A. "May be fatal if swallowed" should be expanded to "May be fatal if swallowed or absorbed through the skin."

   B. "Wash thoroughly after each use." should be expanded to, "Wear protective clothing and rubber gloves. Wash thoroughly with soap and water after handling and before eating, drinking, or using tobacco. Remove contaminated clothing and wash before reuse."

The Toxicity Categories for Danitol 2.4 EC are II for oral toxicity and primary eye irritation, and III for dermal toxicity, inhalation toxicity, and primary dermal irritation. Danitol 2.4 is not a dermal sensitizer in guinea pigs. Considering this toxicity profile, the following label changes are suggested:

1. The label should state that the product is for restricted use only.

2. An additional Precautionary Statement, "Wash thoroughly with soap and water after handling and before eating, drinking, or using tobacco. Remove contaminated clothing and wash before reuse" should immediately follow the sentence "Avoid breathing spray mist."

3. Since Danitol 2.4 is a Category II eye irritant, the Precautionary Statement should be modified to require the wearing of goggles, face shield, or safety glasses.

4. The label does not mention where the product may be used, and therefore does not exclude indoor or greenhouse use. The label should specify outdoor use only.

5. The Note to Physicians mentions that the product contains a [redacted]. Since its concentration exceeds the 10% criteria for inerts (40 CFR § 156.50), it should be identified in the ingredients statement by a common name.

The inerts in Danitol 2.4 EC Spray have been cleared for use. The Insecticide, Rodenticide Branch has no objections to the registration of Danitol technical and Danitol 2.4 EC Spray provided:

1. RD can confirm that the technical product cannot be milled to produce an inhalable aerosol.

2. The end-use product will be classified for restricted use only.

Copies of the proposed labels, an 8-Point Free-Standing Summary, a suggested Dermal Absorption protocol, and Data Evaluation Reports for the submitted studies are attached. Although the submitted dermal absorption study was Unacceptable, it was not needed for this action. If future petitions require dermal absorption data, this protocol should be followed.

SUMMARY OF TOXICITY DATA
and
EIGHT POINT FREE-STANDING SUMMARY

1. Summary of selected toxicology data considered for these actions:

STUDY	RESULTS	TOXICITY CATEGORY	CLASSIFICATION
Data on Technical Danitol (fenpropathrin):			
Acute Oral LD_{50}, Rat	54.0 mg/kg (male) 48.5 mg/kg (female)	I	Minimum
Acute Dermal LD_{50}, Rat	1600 mg/kg (males) 870 mg/kg (females)	II	Minimum
Acute inhalation LC_{50}, Mouse and Rat	The maximum attainable vapor concentration (0.009 ug/l) was nontoxic.	—	Supplementary
Primary Eye Irritation, Rabbit	No corneal involvement. Mild iris and conjunctival irritation.	III	Guideline
Primary Dermal Irritation, Rabbit	Not an irritant.	IV	Guideline
Dermal Sensitization, Guinea Pig	Not a sensitizer		Minimum
Neurotoxicity, Hen	No delayed neurotoxicity at ≤1000 mg/kg/d X 5		Minimum
2-Year Feeding/Oncogenic, Mouse	Systemic NOEL >600 ppm (HDT; M/F 56.0/65.2 mg/kg/d) There were no indications of toxicity or oncogenicity other than marginally increased hyperactivity in females dosed at 600 ppm.		Guideline

006918

STUDY	RESULTS	CATEGORY	CLASSIFICATION
2-Year Feeding/Oncogenic, Rat	Systemic NOEL = 450 ppm (17.06 mg/kg/d) in males 150 ppm (7.23 mg/kg/d) in females Systemic LEL = 600 ppm (HDT; 22.80 mg/kg/d) in males (increased mortality, body tremors, increased pituitary, kidney, and adrenal weights) 450 ppm (19.45 mg/kg/d) in females (increased mortality and body tremors) There was no evidence of oncogenicity at any dose.		Guideline
1-Year Feeding, Dog	Systemic NOEL = 2.5 mg/kg/day Systemic LEL = 6.25 mg/kg/day (tremors in all dogs)		Minimum
Teratology, Rat	Maternal NOEL = 0.4 mg/kg/day Maternal LEL = 2.0 mg/kg/day Fetotoxic NOEL > 10 mg/kg/day (HDT) Teratogenic NOEL > 10 mg/kg/day (HDT)		Minimum
Teratology, Rabbit	Maternal NOEL = 4 mg/kg/day (HDT) Maternal LEL = 12 mg/kg/day (grooming, anorexia, flicking of the forepaws) Fetotoxic NOEL >36 mg/kg/day (HDT) Embryotoxic NOEL >36 mg/kg/day (HDT) Teratogenic NOEL >36 mg/kg/day (HDT)		Guideline
3-Generation Reproduction, Rat	Parents: Systemic NOEL = 40 ppm (M/F 3.0/3.4 mg/kg/day) Systemic LEL = 120 ppm (M/F 8.9/10.1 mg/kg/day) (body tremors with spasmodic muscle twitches, increased sensitivity and maternal lethality) Pups: Reproductive NOEL = 120 ppm (M/F 8.9/10.1 mg/kg/day) Reproductive LEL = 360 ppm (M/F 26.9/32.0 mg/kg/day) - (decreased mean F_{1B} pup weight, increased F_{2B} loss) Fetotoxic NOEL = 40 ppm (M/F 3.0/3.4 mg/kg/day) Fetotoxic LEL = 120 ppm (M/F 8.9/10.1 mg/kg/day) - (body tremors, increased mortality)		Minimum

STUDY	RESULTS	CATEGORY	CLASSIFICATION
Mutagenicity Studies:			
1. Gene Mutation Test:			
Gene Mutation Test in *Salmonella* and *E. Coli*	Negative for *Salmonella* TA98, TA100, TA1535, TA1537, and TA1538; and E. Coli WP2uvrA (trp^-) with or without metabolic activation.		Acceptable
2. Structural Chromosome Aberration Test:	No acceptable data available		
3. Tests for Other Genotoxic Effects:			
In Vitro Sister Chromatid Exchange Test	There were no increases in sister chromatid exchanges seen in CHO-¯1 cells.		Acceptable
DNA Damaging Capacity with *Bacillus subtilis*	Not mutagenic		Acceptable
In Vitro Assay in Mouse Lymphoma cells	Equivocal results - probably of no concern		Acceptable
Metabolism, Rat (2 studies)	97% is eliminated in 48 hours. Little residue after 8 days. Highest concentration in fat. Metabolites were identified in urine.		Minimum
Percutaneous Absorption, Rat	Over a 24-hour period, very little test article was absorbed through the skin. The major route of elimination was the urine.		Unacceptable

2. Summary of Data Considered Desirable but Lacking for This Action:

There is no acceptable Structural Chromosome Aberration Test. An acceptable study should be submitted as soon as possible.

3. Action Being taken to Obtain the Lacking Information or Other Additionally Needed Information:

The requirement for an acute inhalation study using the technical can be waived only if RD can assure tha the product cannot be milled to produce an inhalable aerosol.

4. A Summary of Other Permanent Tolerances Granted for This Herbicide:

No permanent tolerances have been granted.

5. There is no dietary impact from the proposed use of this pesticide since it is for nonfood use.

6. A previously submitted 2-Year Rat Feeding study with a NOEL of 1.0 ppm (0.05 mg/kg/day) was used to set the PADI. The safety factor employed was 100. The PADI is 0.0005 mg/kg/day. The PADI will soon be reconsidered in light of the recently reviewed studies.

7. There are at this writing no pending regulatory actions against the registration of this pesticide.

8. Other Relevant Considerations:

None

Page_____ is not included in this copy.

Pages 8 through 14 are not included.

The material not included contains the following type of information:

_____ Identity of product inert ingredients.

_____ Identity of product impurities.

_____ Description of the product manufacturing process.

_____ Description of quality control procedures.

_____ Identity of the source of product ingredients.

_____ Sales or other commercial/financial information.

✓ A draft product label.

_____ The product confidential statement of formula.

_____ Information about a pending registration action.

_____ FIFRA registration data.

_____ The document is a duplicate of page(s) _____.

_____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.

Procedure for Studying Dermal Absorption

Robert P. Zendzian Ph.D.
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Introduction

This paper presents a general procedure for dermal absorption studies on pesticides which is applicable to any compound or formulation of a compound. The study requires application of various doses of radiolabeled compound to the shaven skin of male rats followed, at specific intervals after dosing, by total urine and fecal collection, determination of blood concentration, determination of the quantity in the body and determination of the quantity remaining on the skin. It is assumed that a metabolism study of the test compound has been performed in the rat before the dermal absorption study is undertaken.

The rat is used for purely practical reasons, it is not intended as a model of absorption through the human skin but rather as a test system for dermal absorption. The domestic rat is a conveniently sized animal, which is readily available and used for most of the toxicology studies on pesticides including metabolism. Because of its small size, several animals can be used per dose and several dose levels per compound within the constraints of time and resorces. Foreign compounds in general pass more rapidly through rat skin than through human skin and thus determination of dermal penetration in the rat offers a built-in safety factor for projection to human exposure.

The study described here combines two different types of dermal absorption studies in a manner which can compensate for their individual deficiencies and simultaneously cover the full range of possible dermal absorption patterns. The first type of study involves placing a measured quantity of compound on the skin for a specific period of time. The animal is then killed and the treated skin is removed. The quantity remaining on the skin is determined and the quantity of compound absorbed is calculated by subtraction. This method works very well for small quantities of a compound which does not fall or vaporize off of the skin. Large quantities, volatile compounds or strange solvents, cannot be used in this procedure.

The second type of study measures what goes into the animal. The compound is applied to the skin in a measured dose and the quantity in the body and the quantity excreted for a specific time period is measured. The procedure has greater possibilities for error in very low doses, for compounds which are not rapidly excreted and for compounds which are completely metabolized to CO_2, water and urea.

Materials

Twenty-four young adult male rats, 225-250 grams in weight, are used at each dose point. It is preferred that the rats be of the same strain used for metabolism studies on the test compound.

The compound should be chemically pure and radiolabeled, usually with carbon-14, in a position which is part of the "core" of the compound. The label should follow the compound and its major metabolites until excreted. The label should not be exchangeable nor should it be metabolically removed to CO_2 or become part of the one-carbon pool of the organism. Double labeling may sometimes be necessary. Unlabeled compound may be used if a sufficiently specific and sensitive test is available.

Methods

Twenty-four hours prior to dosing the back and shoulders of the rats are clipped free of hair and the area washed with acetone. Do not damage the skin.

Twenty-four animals are used per dose. A minimum of three but preferably four doses, at log intervals should be used. The doses should span the range of dose per unit area of skin which can be expected to occur in human exposure. Experience has shown that the highest useful dose is in the order of 10 mg/rat with descending doses of 1, 0.1, and 0.01 mg/rat. If less then four doses are used it is preferred that the lower dose range be used. Doses must be mass/unit area of skin (mg/cm^2) and not mass/body weight (mg/kg) since the rate of absorption is directly related to mass/unit area.

The compound is applied to a measured area of the rat's skin, at least 10 cm^2, in the form applied in the field utilizing the field solvent. Usually the use product (emulsifiable concentrate, flowable powder etc.) is used for the highest dose and is diulted with water for the lower doses. When no solvent is specified, as for the technical material or a dust, the compound is dissolved or suspended in water. Organic solvents should not be used. The material is spread evenly until dry. The spreader should be checked for loss of material. The treated area is covered with a nonocclusive cover to prevent loss by falling or being rubbed off and to prevent the animal eating the test material.

Experience has shown that the application area must be covered. A combination cover consisting of a 'spacer' glued to the skin and a filter paper or gauze glued to the ring appears to be most effective. The 'spacer' will outline the application site and be sufficiently thick to hold the cover from contact with the site.

The treated animals are placed individually in metabolism cages. All urine and feces are collected, a single collection for the entire duration of exposure. At intervals of 1/2, 1, 2, 4, 10 and 24 hours, four animals per dose are anesthetized. The exposed skin and residual compound are collected separately by washing the skin with a mild soap solution followed by several water rinses. Liquid Ivory or Dove for dishwashing is suggested. The skin must be washed before killing the animals, as up to three fold differences have been observed in the ability of skin on the live animal and skin from the killed animal to bind test compounds. The animals are killed, a blood sample taken, and residual urine collected from the bladder and added to the collected urine. Any material on the protective appliance is measured. The remainder of the animal is prepared for determination of the quantity of compound in the carcass.

For each animals the following determinations are made. Results are expressed as quantity or concentration of the parent compound and as percent of applied dose. Metabolites are not separately distinguished.

1) The quantity of the compound in/on the application device and the protective appliance.

2) The quantity of compound that can be washed from the skin.

3) Quantity of compound remaining on/in the skin at the application site which cannot be removed by washing.

4) Concentration of compound in the blood and from this the quantity of compound in the blood.

5) Quantity of compound excreted in the urine and feces.

6) Quantity of material remaining in the carcass.

Results and Conclusions

From the quantity determined in parts 1 and 2 above one may calculate, by subtraction the quantity absorbed provided that other routes of loss are not significant. Excessive variation of results within groups at the same time and dose will indicate external loss of the dose.

From the quantity in the skin, the quantity excreted, the quantity in the blood and the quantity remaining in the carcass one may obtain directly the quantity absorbed. The quantity which cannot be removed from the skin by washing is considered potentially able to be absorbed and, if the amount is large, special studies may be required to quantitate its potential for absorption.

The blood concentration of the compound can be used for a direct comparison with other studies on the compound.

Graphs relating dose, time and amount absorbed may be constructed and used to calculate absorption for doses which are not directly studied. Using proper assumptions one may extrapolate to estimate human absorption under conditions of normal exposure.

Additional procedures

1) Procedure to define compounds which are essentially not absorbed.

Results from a study of a compound expected to have little or no dermal absorption have suggested the necessity of treating an additional group of rats. In the study, analysis of the dermal residue indicated no absorption to a limit of 0.1 percent of the dose. This limit was defined by the variability of recovery of compound from the skin. The blood showed no radioactivity at any dose and duration of exposure. The urine showed radioactivity which did not appear to follow the dose and duration of exposure relationship expected. In only one of nine treatment groups were the results internally consistent with all four animals showing similar positive results. In the other eight groups the number of animals having radioactivity in the urine ranged from zero to three with a mean of 1.5. These results appeared indicative of contamination of the urine rather than dermal absorption.

Under such circumstances an additional group of four rats should be treated with the high dose at the 10 and 24 hour durations of exposure. These animals should have their urinary bladders cannulated to avoid contamination of the urine collected during the exposure period. Samples of blood, urine and carcass should be counted for the longest practical time in order to produce the lowest possible limit of dermal absorption. In the case where no absorption occurs under the experimental conditions the limit of dermal absorption will be defined solely by the sensitivity of the method for detecting the radio tracer.

2) Procedure for examining compounds which show a major residue on/in the washed skin.

Several compounds have been tested which show a significant residue on/in the skin despite vigorous washing. The concentration has appeared in short exposures and shows little or no increase with time and often does not appear to increase to any large extent with increase of dose. This suggests a binding process.

For regulatory purposes one must assume that this material is available for further absorption. However, this may not be true particularly in cases were little or no detectable compound appears in blood, excreta and/or carcass. However, studies such as the one suggested below have shown that absorption of the residue following washing can range from none detectable to essentially all, over a period of two weeks after dosing.

In such cases the following additional study is suggested.

1) Eight rats per dose are treated for the time period which shows the maximum skin concentration (or ten hours).

2) At the end of the exposure period 4 rats per dose are treated as in the basic protocol.

3) The skin of the remaining 4 rats per dose, is washed in the same fashion used in the basic study and the animals followed for at least an additional 72 hours. A study which carried the post-wash period for up to three weeks showed maximum absorption at two weeks. This appears to be a practical limit for observation.

4) The animals are then treated as in the basic protocol.

A balance comparison of the various residues will give some indication as to whether or not the quantity in the washed skin can be absorbed and quantitation of any absorption. If absorption occurs it may be necessary to repeat this process with longer post washed periods to obtain a quantitation of absorption over time.

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Revised
September 18, 1987

Including
California Modifications
October 9, 1985

Please note. This procedure has been developed by the experimental work performed on pesticides by Registrants in their own or contract laboratories. Their continued work provides valuable and unique information on improving the experimental design and methodology. It is strongly advised that you contact the Agency before performing a dermal absorption study on a pesticide in order to take advantage of the most recent information. You may submit your protocol, through the Registration Division, for evaluation by the author of this document.

Reviewed by: John E. Whalan JW 8-22-88
Section II, Tox. Branch (TS-769C)
Secondary reviewer: Edwin R. Budd
Section II, Tox. Branch (TS-769C)

81-3

006918

DATA EVALUATION REPORT

STUDY TYPE: Acute Inhalation in Rats and Mice

ACCESSION NUMBER: 265376

TOX. CHEM. NO.: 273H

TEST MATERIAL: Danitol Technical (SX-1713)
Amber-colored solid

MRID NO.: N/A

SYNONYMS: Fenpropathrin

STUDY NUMBER(S): CEHC 2545

SPONSOR: Sumitomo Chemical America, Inc.

TESTING FACILITY: Chevron Environmental Health Center, Inc.

TITLE OF REPORT: The Acute Vapor Inhalation Toxicity of Danitol Technical (SX-1713) in Mice and Rats

AUTHOR(S): E.D. Bruce, L.C. Griffis, Z.A. Wong

REPORT ISSUED: September 5, 1986

CONCLUSIONS: Although this study was well performed, it was not possible to generate sufficient test article vapor to elicit any toxic response in the test animals.

STUDY CLASSIFICATION: This study is CORE SUPPLEMENTARY. The maximum attainable vapor concentration was used, but it was insufficient to cause any toxicity. The test animals should have been exposed to an aerosol/vapor rather than just a vapor.

Special Review Criteria (40 CFR 154.7): N/A

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PROTOCOL: The test systems used in this study included 10 male (527-586 g) and 10 female (271-291 g) Sprague-Dawley rats (130 days old), and 10 male (36.7-39.6 g) and 10 female (29.6-32.5 g) Swiss-Webster (Crl:CFW® (SW)BR) mice (122 days old). The 5 rats/sex and 5 mice/sex were simultaneously exposed for 4 hours to the highest attainable concentration of vaporized Danitol technical (94.5% purity) in a 0.42 m^3 dynamic inhalation chamber. The vapor was generated by melting the test article in a nebulizer to 58-60° C. The resulting vapor and aerosol were introduced into an airstream, passed through an equilibration chamber, then passed through a HEPA filter to remove all aerosol before entry into the inhalation chamber. Thus, the animals were dosed with a saturated vapor free of aerosol particles. Additional groups of rats and mice were similarly exposed to air only and served as nontreated controls. Food and water were available ad libitum except during exposure.

The concentration of the vapor was determined by passing chamber atmosphere near the animals' breathing zone through acetone bubblers. The acetone was

them measured for collected test article. In addition, gravimetric measurements of aerosol in the equilibration chamber were made. Particle sizing was not performed since the test article was administered as a vapor.

All animals were observed for clinical signs during the exposure and at least once daily thereafter. They were weighed prior to dosing, and on days 2, 7, and 14. At the end of the 14-day study, all survivors were sacrificed and grossly examined. The lungs and tracheae of each animal were evaluated histopathologically.

RESULTS: The mean gravimetric aerosol concentration in the equilibration chamber (the mixing chamber prior to filtration and chamber introduction) was 0.82 mg/l. The analytical concentration of vapor in the breathing zone of the animals was 0.009 ug/l. None of the control or treated animals had any clinical signs, and body weight increases were similar. No compound-related gross or microscopic lesions were found in any rats or mice. The absence of toxicity was due to the miniscule vapor concentration attainable as a result of the test article's low vapor pressure.

Reviewed by: John E. Whalan JW 8-22-88
Section II, Tox. Branch (TS-769C)
Secondary reviewer: Edwin R. Budd
Section II, Tox. Branch (TS-769C)

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006918

DATA EVALUATION REPORT

STUDY TYPE: Chronic Feeding/Oncogenicity in Rats

ACCESSION NUMBER: 265377-265382 (6 volumes)

TOX. CHEM. NO.: 273H

TEST MATERIAL: Danitol (S-3206)
Batch 01113 (91.4% pure)
Batch 20514 (92.5% pure)
Brown waxy solid or brown liquid

MRID NO.: N/A

SYNONYMS: Fenpropathrin

STUDY NUMBER(S): SMO 167/851348

SPONSOR: Sumitomo Chemical Co., Ltd. (Sumitomo No. FT-61-0161)

TESTING FACILITY: Huntingdon Research Centre (England)

TITLE OF REPORT: Potential Tumorigenic and Toxic Effects in Prolonged Dietary Administration to Rats (Final Report)

AUTHOR(S): Simon Warren, Ralph Heywood, Alan E. Street, Chirukandath Gopinath, J.G.L. Browne, W.A. Gibson, L.E. Reed, A. Anderson

REPORT ISSUED: July 15, 1986

CONCLUSIONS: An MTD level was administered in this study as evidenced by the increased mortality. The defined doses are as follows:

Systemic NOEL = Males - 450 ppm (17.06 mg/kg/day)
Females - 150 ppm (7.23 mg/kg/day)

Systemic LEL = Males - 600 ppm (22.80 mg/kg/day) - Increased mortality, body tremors, increased pituitary, kidney, and adrenal weights.

Females - 450 ppm (19.45 mg/kg/day) - increased mortality and body tremors.
At 600 ppm (23.98 mg/kg/day) the females had impaired food efficiency, decreased ovary weights, and increased adrenal weights.

There was no evidence of oncogenicity at any dose up to and including 600 ppm (22.80 and 23.98 mg/kg/day in males and females, respectively).

STUDY CLASSIFICATION: This study is classified CORE GUIDELINE. Stability and homogeneity analyses were performed during a preliminary study, but the results were not reported. This study received Quality Assurance Review.

Special Review Criteria (40 CFR 154.7): N/A

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22

PROTOCOL: A total of 365 male (205-288 g) and 365 female (132-192 g) CD rats (approximately 42 days old) were randomly assigned to groups of 50/sex/group, and 15/sex/group; the smaller groups served as satellites and were designated for interim sacrifices. The rats were group housed 5 to a cage. Food and water were available ad libitum. They were dosed with technical Danitol which was dispersed in corn oil and formulated into the diet weekly. The doses given were 0 (vehicle controls), 50, 150, 450, and 600 ppm of active ingredient. The vehicle control rats were dosed with a volume of corn oil in the diet, which was equivalent to the volume given to the dosed rats. The dose formulations were analyzed for dose concentration at regular intervals throughout the study. Stability and homogeneity analyses were performed during a preliminary study; the results were not reported in this study.

All rats were observed twice daily for mortality. During the first 14 weeks, observations of clinical signs and palpations for tumors were made daily, but in the absence of significant events, these observations were cut back to once weekly. The rats were weighed on weeks -2, -1, on the day of dosing, and weekly thereafter. Food consumption was measured weekly for each cage of rats. Calculations were made to determine food efficiency and test material intake. Measurements of water consumption over a 5 day period were made during weeks 24, 50, 76, and 104 for the control and high-dose rats. Ophthalmologic examinations of the control and high-dose rats were conducted prior to dosing, and during weeks 6, 13, 26, 52, 78, and 104. The eyes of all groups were examined during week 106. The following clinical pathology parameters were evaluated:

Hematology

- Erythrocytes
- Hemoglobin
- Hematocrit
- Mean corpuscular hemoglobin concentration
- Mean cell volume
- Reticulocytes (week 52 males only)
- Leukocytes (total and differential)
- Platelets
- Abnormal cells
- Thrombotest (first test at week 26)

Clinical Chemistry

- Alkaline phosphatase
- SGOT
- SGPT
- LDH (week 107 instead of 104)
- Bilirubin, total
- Cholesterol
- Blood urea nitrogen
- Creatinine
- Total protein
- Albumin
- Globulin
- Glucose
- Sodium
- Potassium
- Calcium
- Phosphorus, inorganic
- Chloride

Urinalysis

- pH
- Specific gravity
- Volume
- Protein
- Reducing substances
- Hemoglobin
- Cells (epithelial, erythrocytes, polymorphonuclear and mononuclear leukocytes)
- Organisms

Glucose
Ketones
Bile pigments

Casts
Abnormal constituents

Orbital sinus blood and urine samples were obtained from 10 satellite rats/sex/group at weeks 25/26, and 51/52 (some main study rats were sampled when mortality was high among the satellite rats). Samples were collected from 10 main study rats/sex/group at weeks 77/78 and 103/104. LDH analyses were omitted during week 104, but were repeated during week 107.

The surviving satellite rats used for clinical pathology measurements were all sacrificed after being sampled at week 52 and thus became interim sacrifice animals. The main study rats were sacrificed as follows:

Dose (ppm)	Study Duration (weeks) Male	Female
0, 50, 150, 450	108	115
600	108	52

A 75% mortality criteria was used for choosing the sacrifice intervals for the main study rats, and this was the justification for terminating the high-dose main study females. All rats, including those sacrificed moribund, were examined grossly with particular attention to tumor formation. The following list of tissues were examined. Those marked with asterisks (*) were weighed. Those underlined were examined histopathologically for all main group rats. Those marked with a cross (†) were examined in the animals sacrificed at the interim and terminal sacrifices.

†Abnormal tissue
*Adrenals
Bone (femur, sternum)
Bone marrow (sternal)
†*Brain
Cecum
Colon
Duodenum
Esophagus
Eyes
Harderian gland
Head (nasal cavity, paranasal sinuses, buccal cavity, middle ear, nasopharynx, teeth, lacrimal and Zymbal's glands)
*Heart
Ileum
Jejunum
*Kidneys
*Liver
Lungs (with bronchi)
Lymph nodes (cervical and mesenteric)
Mammary gland
†Nerve (L & R of plantar, sciatic, tibial, trigeminal ganglion, dorsal ganglion of sciatic nerve)
*Ovaries
Pancreas
*Pituitary
Prostate
Rectum
Salivary gland
Seminal vesicles
Skeletal muscle
Skin
†Spinal column and cord (cervical, thoracic, lumbar)
Spleen
Stomach
*Testes (with epididymides)
Thymus
*Thyroid and parathyroid
Trachea
Urinary bladder
Uterus (corpus, cervix)

24

RESULTS: Dose concentration analyses measured the test article concentration to be within 13.3% of nominal; most analyses were comfortably within 10% of nominal. Stability and homogeneity analyses were performed in the course of another study; the results were not reported. Adjustments of the test article formulation were not made to compensate for decreased food consumption over time. The daily doses (in units of mg/kg/day) consumed during the first 13 weeks were approximately double those consumed during the last year of the study. The calculated group mean doses were as follows:

Concentration	Dose (mg/kg/day) Male	Female
50 ppm	1.93	2.43
150 ppm	5.71	7.23
450 ppm	17.06	19.45
600 ppm	22.80	23.98

Mortality during the first 26 weeks was greatest in the females at the 450 and 600 ppm doses. All the surviving 600 ppm females were terminated at the one year mark. During the remainder of the study, mortality was not dose-related. The following table presents the mortality pattern:

	Dose (ppm)	Main Groups Male	Female	Satellite Groups Male	Female
WEEKS 1-26:	0	0/50	0/50	0/15	0/15
	50	2/50	0/50	0/15	0/15
	150	0/50	0/50	0/15	1/15
	450	1/50	8/50	0/15	3/15
	600	5/50	23/50	2/15	8/15
WEEKS 27-52:*	0			0/15	0/15
	50			1/15	0/15
	150			0/15	0/14
	450			0/15	0/12
	600	19/45	-	0/13	0/7
WEEKS 27-Termination:	0	35/50	34/50		
	50	25/48	37/50		
	150	31/50	35/50		
	450	26/49	22/42		
	600	19/45	-		

* The surviving 600 ppm main study females and all the satellite groups were sacrificed at 52 weeks.

The only dose-related clinical sign was body tremors, which were seen in the 600 ppm males (≤ 6% affected between weeks 1 and 10), the 450 ppm females (≤ 5% affected between weeks 1 and 14), and 600 ppm females (≤ 65% affected between weeks 1 and 52). These tremors occurred primarily in the morning. Body weight gain, food consumption, and water consumption were similar for all main groups. The food conversion ratio was increased for the 600 ppm

25

females because of impaired efficiency, but was similar for all other groups. There were no compound-related ophthalmologic lesions, and no dose-related clinical pathology anomalies. Many of the rats had symptoms of a viral infection between weeks 30 and 33, but there were no indications of an adverse effect on the study.

Organ weight anomalies observed in the satellite groups included an increase in absolute and relative kidney weights in the 600 ppm males, and an increase in absolute and relative adrenal weights in the females. In the main study, the 600 ppm males had nearly a doubling in the absolute and relative pituitary weights, and significant increases in absolute and relative kidney and adrenal weights; and the 600 ppm females had decreased absolute and relative ovary weights.

There were no compound-related gross lesions found in either sex. Only age-related histopathologic lesions were found, with slightly greater incidence in the high-dose groups. There was evidence of minimal axonal degeneration in all groups (following table), but there was no correlation between clinical findings of tremor in the higher doses and microscopic findings of axonal degeneration. It is curious that nearly as many control animals should have degeneration as the dosed groups, since this is not characteristic in senescent rats (consulted with L.J. Slaughter, DVM - pathologist).

	0 ppm	50 ppm	150 ppm	450 ppm	600 ppm
MALES:					
Axonal degeneration,					
Spinal cord	26/50	33/50	32/50	32/50	40/50
Sciatic nerve	35/50	39/50	36/50	35/50	41/50
Tibial nerve	12/15	22/23	18/19	23/23	26/27
FEMALES:					
Axonal degeneration,					
Spinal cord	30/50	29/50	31/50	31/50	-
Sciatic nerve	36/50	39/50	37/50	35/50	-
Tibial nerve	13/16	10/13	13/15	17/20	-

The neoplastic lesions were generally not dose-related, of minor incidence, and reportedly within historic levels. The females dosed at 600 ppm were relatively free of neoplastic lesions since the group was terminated after only 52 weeks. Both males and females had relatively high incidences of anterior pituitary adenoma which were not compound-related, but were nevertheless responsible for some of the deaths. The following table summarizes the major tumor incidences:

	0 ppm	50 ppm	150 ppm	450 ppm	600 ppm
MALES:					
Pituitary,					
Adenoma of pars ant.	25/50	17/50	22/50	17/50	19/50
Carcinoma of pars ant.	0/50	0/50	0/50	0/50	1/50

	0 ppm	50 ppm	150 ppm	450 ppm	600 ppm
FEMALES:					
Pituitary,					
Adenoma of pars ant.	36/50	34/50	35/50	25/50	-
Carcinoma of pars ant.	2/50	0/50	1/50	3/50	-
Mammary gland,					
Fibroadenoma	33/36	37/39	28/37	34/36	-
Adenoma	1/36	0/39	0/37	2/36	-
Adenocarcinoma	8/9	14/16	8/9	9/10	-

Reviewed by: John E. Whalan JW 8-22-88
Section II, Tox. Branch (TS-769C)
Secondary reviewer: Edwin R. Budd
Section II, Tox. Branch (TS-769C)

83-1,2

006918

DATA EVALUATION REPORT

STUDY TYPE: Chronic Feeding/Oncogenicity in Mice [Terminated after 13 Weeks]

ACCESSION NUMBER: 265388

TOX. CHEM. NO.: 273H

MRID NO.: N/A

TEST MATERIAL: Technical Danitol (S-3206)
Batch No. 01113 (91.4% pure)
Yellowish, brown crystalline solid

SYNONYMS: Fenpropathrin

STUDY NUMBER(S): SMO 122/82228

SPONSOR: Sumitomo Chemical America, Inc.

TESTING FACILITY: Huntingdon Research Centre (England)

TITLE OF REPORT: S-3206 Two-Year Feeding Study in Mice: (Terminated After 13 Weeks of Treatment)

AUTHOR(S): J.C. Colley, P.J. Welch, R. Haywood, D.E. Prentice, W.A. Gibson
C.P. Cherry, S.K. Majeed, R.H. Almond

REPORT ISSUED: November 6, 1982

CONCLUSIONS: There was a 15.2% increase in mortality in the highest dose tested (1000 ppm). The cause of death was generally not known, but many mice had neurologic signs including body tremors.

STUDY CLASSIFICATION: Core Supplementary. This study was not reviewed in depth because the report for the chronic study was available.

Special Review Criteria (40 CFR 154.7): N/A

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A total of 403 male and 420 female CD-1 mice (42 days old) from Charles River, Manston, England were randomly assigned to groups of 52/sex/group, and 40/sex/group; the smaller groups served as satellites and were designated for interim sacrifices. They were dosed with technical Danitol (S-3206) which was dispersed in corn oil and formulated into the diet. The doses given and the resulting mortalities during the aborted 13 week study were as follows:

Dose (ppm)	Dose (mg/kg/day) Male	Dose (mg/kg/day) Female	Mortality Male	Mortality Female	Mortality Total
0	0.0	0.0	2/92 (2.2%)	0/92 (0%)	2/184 (1.1%)
40	4.9	5.7	1/92 (1.1%)	1/92 (1.1%)	2/184 (1.1%)
200	24.7	27.8	4/92 (4.3%)	0/92 (0%)	4/184 (2.2%)
1000	130.0	139.0	20/92 (21.7%)	8/92 (8.7%)	28/184 (15.2%)

The mortality table includes a few animals which were sacrificed moribund. The final report stated that several high-dose males and one mid-dose male had occasional body tremors beginning after the first week. In addition, slightly higher food consumption and weight gain were found in the mid and high-dose males, and slightly higher liver weights were found in high-dose males and females. There was evidence of cage fighting and cannibalism in many of the mice as a result of group-housing. The causes of death were not established for most animals.

This study was aborted at 13 weeks because of high mortality, and repeated at doses of 0, 40, 150, and 600 ppm. The maximum dose in the repeat study (600 ppm) seems appropriate based on 15.2% mortality seen at a dose of 1000 ppm. The review of the repeat study follows.

Reviewed by: John E. Whalan JW 8-22-88
Section II, Tox. Branch (TS-769C)
Secondary reviewer: Edwin R. Budd
Section II, Tox. Branch (TS-769C)

83-1,2

306918

DATA EVALUATION REPORT

STUDY TYPE: Chronic Feeding/Oncogenicity in Mice

ACCESSION NUMBER: 265383-265387 (5 volumes)

TOX. CHEM. NO.: 273H

TEST MATERIAL: Technical Danitol (S-3206)
Batch 01113 (91.4% pure)
Batch 20514 (92.5% pure)
Yellowish brown crystalline solid

MRID NO.: N/A

SYNONYMS: Fenpropathrin

STUDY NUMBER(S): SMO 149/84607

SPONSOR: Sumitomo Chemical America, Inc.

TESTING FACILITY: Huntingdon Research Centre (England)

TITLE OF REPORT: S-3206 Two-Year Feeding Study in Mice

AUTHOR(S): J. Colley, R. Haywood, A.E. Street, C. Gopinath, J.M. Offer, W.A. Gibson

REPORT ISSUED: December 3, 1985

CONCLUSIONS: The high-dose females dosed with 600 ppm (65.2 mg/kg/day) of technical Danitol had marginally increased hyperactivity prior to week 78. This is an event of minor significance. No other indications of toxicity or carcinogenicity were seen. The NOEL for chronic toxicity is defined as >600 ppm (56.0 and 65.2 mg/kg/day in males and females, respectively), which is the highest dose tested. There was no evidence of oncogenicity at this dose.

STUDY CLASSIFICATION: This study is Core GUIDELINE. It was a well run and documented study. Organ weight data were presented as absolute values only; relative organ weight tables should have been included. This study received Quality Assurance review. Because of the overall lack of toxic response at the doses tested, this study might normally be rejected for failing to attain a maximum tolerated dose (MTD). The aborted mouse oncogenicity study (Report No. SMO 122/82228), however, demonstrated that at a slightly higher maximum dose of 1000 ppm, the test article was lethal to 15% of the mice after only 13 weeks. Thus, the maximum dose used in the completed study (600 ppm) was very close to the MTD. A repeat study is not justified.

Special Review Criteria (40 CFR 154.7): N/A

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PROTOCOL: A total of 424 male (19-34 g) and 413 female (17-29 g) CD-1 mice (approximately 42 days old) from Charles River, Manston, England were randomly assigned to groups of 52/sex/group, and 40/sex/group; the smaller groups served as satellites and were designated for interim sacrifices at 26, 52, and 78 weeks. The mice were group housed 4 to a cage. Powdered food and water

were available ad libitum. They were dosed with technical Danitol which was dispersed in corn oil and formulated into the diet weekly. The doses given were 0 (vehicle controls), 40, 150, and 600 ppm of active ingredient. The vehicle control mice were dosed with 0.2-0.3% corn oil in the diet, which was equivalent to the volume given to the dosed mice. The dose formulations were analyzed for stability, homogeneity, and dose concentration at regular intervals throughout the study. The duration of the study was 104 weeks.

All mice were observed daily for mortality. During the first 4 weeks, observations of clinical signs and palpations for tumors were made daily, but in the absence of significant events, these observations were cut back to once weekly. The mice were weighed on day -7, on the first day of dosing, and weekly thereafter. Food consumption was measured weekly for each cage of mice. Calculations were made to determine food efficiency and test material intake. Measurements of water consumption over a 5 day period were made during weeks 24, 50, 76, and 104 for the control and high-dose mice. The following clinical pathology parameters were evaluated:

Hematology

Erythrocytes
Hemoglobin
Hematocrit
Mean corpuscular hemoglobin concentration
Mean cell volume
Leukocytes (total and differential)
Platelets
Abnormal cells

Clinical Chemistry

Alkaline phosphatase
SGOT
SGPT
Blood urea nitrogen
Total protein
Albumin
Globulin
Glucose

Urinalysis

pH
Specific gravity
Volume
Protein
Reducing substances
Glucose
Ketones
Bile pigments
Hemoglobin
Cells (epithelial, erythrocytes, polymorphonuclear and mononuclear leukocytes)
Organisms
Casts
Abnormal constituents

Ten males and 10 females from each satellite group were bled from the orbital sinus at weeks 25, 53, and 79 for the hematology measurements, and at weeks 24, 53, and 79 for the clinical chemistry measurements. Urine samples were collected overnight from 10 male and 10 female fasted satellite mice/group at weeks 26, 51, and 77. The satellite mice used for clinical pathology measurements were sacrificed after being sampled at weeks 26, 52, and 78 weeks, and thus became interim sacrifice animals. Terminal measurements of hematology, clinical chemistry, and urinalysis at week 104 were made for 10 male and 10 female main study mice. All surviving mice were sacrificed at week 104. All mice, including those sacrificed moribund, were examined grossly with particular attention to tumor formation. This was followed with histopathologic

evaluation of the following tissues for all mice (those organs marked with an asterisk were also weighed):

*Adrenals	*Heart	Seminal vesicles
Bone	Ileum	Skeletal muscle
*Brain (medullary, cerebellar, and cortical sections)	Jejunum	Skin
Cecum	*Kidneys	Spinal cord (2 levels)
Colon	*Liver (two lobes)	*Spleen
Duodenum	*Lungs	Sternum (w/ bone marrow)
Esophagus	Lymph nodes (cervical and mesenteric)	Stomach (glandular and nonglandular)
Eyes	Mammary gland	*Testes
Gall bladder	*Ovaries	Thymus
Harderian gland	Pancreas	Thyroid and parathyroid
Head (nasal cavity, paranasal sinuses, tongue, buccal cavity, nasopharynx, middle ear)	Pituitary	Trachea and bronchi
	Prostate	Urinary bladder
	Salivary gland	Uterus (w/ cervix)
	Sciatic nerve	Abnormal tissue

RESULTS: Chemical analyses determined that the test article was stable for at least 18 days at room temperature, and dosing formulations were sufficiently homogeneous. Dose concentration analyses showed the test article concentrations to be within 13.3% of nominal; most analyses were comfortably within 10% of nominal.

As expected, mortality was highest during the final quarter of the study, but the incidence was similar in all dosed and control groups. The mortality pattern was as follows:

Concentration	— Mortality — Male	Female
0 ppm	24/52	23/52
40 ppm	31/52	23/52
150 ppm	23/52	33/52
600 ppm	24/52	28/52

The only clinical sign reported was marginally increased hyperactivity in the high-dose females prior to week 78. Body weight gain, food consumption, food efficiency, and water consumption (measured for controls and high-dose mice only) were similar for all groups. Test material intake was sufficiently constant throughout the study in all dose groups. The calculated group mean doses were as follows:

Concentration	Dose (mg/kg/day) Male	Female
0 ppm	0.0	0.0
40 ppm	3.9	4.2
150 ppm	13.7	16.2
600 ppm	56.0	65.2

There were few clinical pathology anomalies found in the satellite groups. At week 25, the mid and high-dose males had mild neutrophilia, while the low, mid, and high-dose females had moderate neutropenia. At week 10o, the high females were mildly anemic. Aside from several spontaneous clinical chemistry anomalies, the only dose-related effect was a mild decrease in globulin in males at weeks 53 and 79, and in females at weeks 79 and 106; in the absence of other indications of liver toxicity, this is considered a random event. There were no compound-related urinalysis anomalies. Thus, the clinical pathology anomalies discussed were either spontaneous events, or indicators of trends that may have been expressed to a significant degree if higher doses had been used.

There were no compound-related non-neoplastic gross lesions found in either the main or satellite mice. The mice that died or were sacrificed moribund showed typical signs of aging, none of which could be attributed to the test article. There were no compound-related histopathologic lesions in the satellite or main study mice. Absolute organ weight anomalies included increased ovary weights (2.6X) in the high-dose satellite females at week 27, and mildly increased kidney weights in the high-dose satellite males (week 53) and females (weeks 79 and 105). The elevated group ovary weights were skewed by two outliers. In the absence of histopathologic lesions in the ovaries or kidneys of the satellite mice, these findings are considered spontaneous occurrences and not necessarily compound-related.

There were slight increases in hepatic benign tumors and pulmonary adenoma and adenocarcinoma, but the incidence levels were within historical limits, and not always dose-related. Statistical analyses of the pulmonary tumors were misleading since the control values were low compared to historical values (adenoma: 8-10% vs. 0-29% for historical controls, and adenocarcinoma: 2% vs. 2-23% for historical controls). Consultations with L.J. Slaughter, D.V.M. (pathologist) and Richard Levy (statistician) bore this out. Thus, there were no compound-induced neoplasia. The following table tabulates mice with tumors in the organs considered to be synthetic pyrethroid target organs.

	0 ppm	40 ppm	150 ppm	600 ppm
MALES (2 year):				
Lung,				
Pulmonary adenoma	5/52	6/52	6/52	11/52
Pulmonary adenocarcinoma	1/52	6/52	12/52	5/52
Liver,				
Benign liver cell tumor	2/52	3/52	9/52	6/52
Malignant liver cell tumor	12/52	6/52	14/52	8/52
FEMALES (2 year):				
Lung,				
Pulmonary adenoma	4/52	8/52	6/52	2/52
Pulmonary adenocarcinoma	1/52	7/52	4/52	5/52
Liver,				
Benign liver cell tumor	1/52	0/52	1/52	3/52
Malignant liver cell tumor	1/52	1/52	0/52	1/52

Reviewed by: John E. Whalan JW 8-22-88
Section II, Tox. Branch (TS-769C)
Secondary reviewer: Edwin R. Budd
Section II, Tox. Branch (TS-769C)

83-3

006918

DATA EVALUATION REPORT

STUDY TYPE: Teratology Study in Rabbits

ACCESSION NUMBER: 265389

TOX. CHEM. NO.: 273H

TEST MATERIAL: Technical S-3206
Batch No. 20514

MRID NO.: N/A

SYNONYMS: Fenpropathrin

STUDY NUMBER(S): SMO 181/84667

SPONSOR: Sumitomo Chemical America, Inc. (Sumitomo No. FT-51-0134)

TESTING FACILITY: Huntingdon Research Centre (England)

TITLE OF REPORT: The Effect of S-3206 on Pregnancy of the New Zealand White Rabbit

AUTHOR(S): D.C. Cozens, E.W. Hughes, R.E. Masters, and A. Anderson

REPORT ISSUED: November 13, 1985

CONCLUSIONS: There were no compound-related effects on reproduction, and no dose-related effect on the incidence or types of malformations and anomalies observed. The following are the defined doses for this study:

Maternal NOEL = 4 mg/kg/day
Maternal LEL = 12 mg/kg/day [Grooming, anorexia, flicking of the forepaws]
Fetotoxic NOEL >36 mg/kg/day
Embryotoxic NOEL >36 mg/kg/day
Teratogenic NOEL >36 mg/kg/day
A/D Ratio (Adult/Developmental Ratio = Maternal LEL/Teratogenic LEL) =
12 mg/kg/day/>36 mg/kg/day = <0.33

STUDY CLASSIFICATION: This study is classified CORE GUIDELINE. It received Quality Assurance review.

Special Review Criteria (40 CFR 154.7): N/A

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PROTOCOL: This study was performed in three parts, a pilot study to establish dose levels, a preliminary study, and a teratology study. The test article, S-3206 (92.5% pure), was formulated daily by heating it to 80°C. and then diluting it with corn oil vehicle. The dose volume for all studies was 0.5 ml/kg.

In the Pilot Study, 4 groups of 2 nonpregnant female New Zealand rabbits each (26-31 weeks old) were given seven daily administrations of S-3206 by gastric intubation at doses of 20, 30, 45, and 67.5 mg/kg/day. Dosing began on days 0, 3, 5, and 7, respectively. The rabbits were observed and weighed daily, then sacrificed after 7 days of treatment.

34

In the Preliminary Study, 5 groups of 6 nonpregnant female New Zealand rabbits each (14-17 weeks old) were given 13 daily administrations of S-3206 by oral gavage at doses of 0 (vehicle control), 15, 22, 33, and 50 mg/kg/day. Dosing began on day 0. Each formulation was analyzed for dose concentration.

The rabbits were observed daily. They were weighed twice pretest, once prior to dose initiation, and daily during the study. Food consumption was measured over the course of the study. All rabbits were sacrificed 8 days after the final dosing, and examined grossly.

In the Teratology Study, 4 groups of nonpregnant female New Zealand rabbits (14-17 weeks old) were mated with males of proven fertility. An hour after coitus, the does were dosed with Chorulon® lutenizing hormone to assure ovulation. The groups initially consisted of 18, 17, 19, and 17 rabbits, respectively. They were given 13 daily administrations of S-3206 by oral gavage on gestation days 7 through 19 at doses of 0 (vehicle control), 4, 12, and 36 mg/kg/day. Each dose formulation was analyzed for dose concentration.

The rabbits were observed daily, and weighed on gestation days 1, 7, 11, 15, 20, 24, and 29. Food consumption was measured between the weighing intervals. The does were sacrificed on day 29 by cervical dislocation and examined grossly. Their ovaries and uteri were examined for corpora lutea, live young, embryonic and fetal deaths, fetal weights, and fetal abnormalities.

The live young were weighed and sexed, then sacrificed with sodium pentobarbitone for visceral examination. Microdissection and histopathologic evaluation were used as needed to better describe a finding. The pups were then skinned, eviscerated, and fixed in 74°OP industrial methylated spirit. The heads were sliced along the frontoparietal suture line, and examined for gross abnormalities. The carcasses were then clarified, stained by a modified Dawson technique, and examined for skeletal defects.

RESULTS:

Pilot Study - Dose-related clinical signs included nasal or eye exudate, anorexia, grooming, flicking of the forepaws, tremors or shaky movement, and unsteadiness. One rabbit each at the 30 and 67.5 mg/kg/day doses had yellow stained perianal fur, and a 45 mg/kg/day rabbit had an enlarged liver with subcapsular pale areas. Body weight gain was not significantly altered. Abscesses were found in some animals, but in the absence of a control group the significance of these lesions is uncertain.

Preliminary Study - Dose-related clinical signs seen in the preliminary study included grooming, anorexia, flicking of the forepaws, scratching and chewing of the cage, tremors and shaky movements, and unsteadiness. Neither body weight gain nor food consumption were significantly altered. The observed gross lesions were probably not compound-related.

Teratology Study - Dose-related clinical signs included grooming, anorexia, flicking of the forepaws, flicking of the hind feet, shaky movements and trembling, stamping of the hind feet, and lethargy. Neither body weight gain nor food consumption were significantly altered. There were no compound-related gross lesions. There was one death and several dams were sacrificed moribund, but no deaths were attributed to treatment. The following tables present the status of the dams and offspring:

Dose (mg/kg/day)	Mated/ Gravid*	Implants Per Dam	Live Young Per Dam	-Embryonic Deaths- Early	Late	Abortions	Implantation Loss Pre %	Post %
0	15/15	9.5	8.5	0.3	0.6	0	17.6	10.2
4	15/13	8.9	7.8	0.7	0.5	0	13.8	13.2
12	15/15	9.3	8.5	0.1	0.6	0	9.7	10.1
36	15/13	9.1	8.5	0.2	0.5	1	15.3	7.7

Dose (mg/kg/day)	Fetuses Examined	Mean Fetal Weight (g)	% Male	Total Malformations	Total Anomalies Visceral	Skeletal
0	128	43.4	56	1	8	19
4	101	44.8	51	1	6	24
12	127	43.5	48	0	4	20
36	110	43.5	57	0	4	21

* Several does were replaced prior to treatment, found dead, sacrificed moribund, or excluded from the study due to congenital abnormality. These values represent the population status as of day 29.

One high-dose dam was not pregnant at day 29, and another dam aborted. These findings are probably not significant since all other data show that there were no compound-related effects on reproduction. There was also no dose-related effect on the incidence or types of malformations and anomalies observed.

Reviewed by: John E. Whalan JW 7-22-88
Section II, Tox. Branch (TS-769C)
Secondary reviewer: Edwin R. Budd
Section II, Tox. Branch (TS-769C) Budd 8/23/88

83-4

006918

DATA EVALUATION REPORT

STUDY TYPE: 3-Generation Reproduction Study in Rats

ACCESSION NUMBER: 265390

TOX. CHEM. NO.: 273H

TEST MATERIAL: Technical S-3206
Batch 20514

MRID NO.: N/A

SYNONYMS: Fenpropathrin

STUDY NUMBER(S): SMO 164/85707

SPONSOR: Sumitomo Chemical America, Inc. (Sumitomo No. FT-61-0159)

TESTING FACILITY: Huntingdon Research Centre Ltd. (England)

TITLE OF REPORT: Effect of S-3206 on Multiple Generations of the Rat

AUTHOR(S): David D. Cozens, Stephen J. Barton, John M. Offer, William A. Gibson, and Alan Anderson

REPORT ISSUED: June 26, 1986

CONCLUSIONS: The defined doses are as follows:

Parents:

Systemic NOEL = 40 ppm (3.0 mg/kg/day, males; 3.4 mg/kg/day, females)
Systemic LEL = 120 ppm (8.9 mg/kg/day, males; 10.1 mg/kg/day, females) - (body tremors with spasmodic muscle twitches, increased sensitivity, increased maternal lethality)

Pups:

Reproductive NOEL = 120 ppm (8.9 mg/kg/day, males; 10.1 mg/kg/day, females)
Reproductive LEL = 360 ppm (26.9 mg/kg/day, males; 32.0 mg/kg/day, females) - (decreased mean F_{1B} pup weight, increased F_{2B} pup loss)
Fetotoxic NOEL = 40 ppm (3.0 mg/kg/day, males; 3.4 mg/kg/day, females)
Fetotoxic LEL = 120 ppm (8.9 mg/kg/day, males; 10.1 mg/kg/day, females) - (body tremors, increased mortality)

STUDY CLASSIFICATION: CORE MINIMUM. There were no clinical signs reported for the males; there is no way to determine whether they were observed. Softwood bedding (spruce and pine) was used; there was no way to ascertain any effect on hepatic enzyme induction. The histopathology data were not fully interpretable. Dose concentration analyses demonstrated that there were some errors in formulation, but the anomalies probably did not affect the quality of the study. This study received Quality Assurance review.

Special Review Criteria (40 CFR 154.7): N/A

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37

PROTOCOL: The animals used in this study were dosed with S-3206 (92.5% pure) in their feed. The feed was formulated weekly by heating S-3206 to 80°C, mixing it with corn oil, and then with sieved feed. Dose concentrations were measured for each dose level at ten week intervals. Diet stability and homogeneity were assessed during a preliminary study. Food (containing the test article) and water were available ad libitum throughout the study. The diet formulations were not adjusted to compensate for growth. The doses used throughout the study were 0 (vehicle control), 40, 120, and 360 ppm.

Groups of 28 male (164-211 g) and 28 female (124-171 g) Specific Pathogen Free (CrL:COBS CD (SD) BR strain) 6 week old rats were randomly assigned to four groups, and served as the F_0 generation. Mating commenced after 91 days by housing one male with each female for a period of 20 days. Successful mating was determined by vaginal smear. Evidence of sperm or a vaginal plug established the first day of gestation. Females which did not conceive were again mated 7 weeks later.

The F_0 dams reared their pups for 4 days before the litters were culled to 8 pups (4 pups/sex if possible). Unneeded pups were examined grossly. On lactation day 21, the pups were weaned, and 24 pups/sex/dose were selected to constitute the F_{1A} population. They were dosed with the formulated feed. Another male and female from each litter (if possible) were retained for organ weight measurement and tissue preservation. All other pups were sacrificed and examined grossly.

The following tissues were preserved during the course of this study (those marked with a cross were weighed, and those marked with an asterisk were examined histopathologically):

†* Adrenals
Aorta
* Bone marrow (sternal)
* bone (femur)
†* Brain
Cranial vault (lacrymal glands, teeth, nasal turbinates, inner ear)
* Cecum
Colon
* Duodenum
* Eyes
†* Heart
* Ileum
Jejunum
†* Kidneys
†* Liver
†* Lungs
* Lymph Nodes (cervical and mesenteric)
Mammary gland
Esophagus
†* Ovaries
* Pancreas
†* Pituitary
†* Prostate (with seminal vesicles)
* Salivary gland
Sciatic nerve
Skeletal muscle
Skin
Spinal column
†* Spleen
* Stomach
†* Testes (with epididymides)
†* Thymus
†* Thyroids
Tongue
Trachea
* Urinary bladder
†* Uterus (with vagina)

Ten days after the F_{1A} pups were weaned, the F_0 population was again mated. The dams reared their F_{1B} pups for 4 days before the litters were culled to 8 pups (4 pups/sex if possible). Unneeded pups were examined grossly. On lactation day 21, the F_{1B} pups were weaned, and 24 pups/sex/dose were selected

to represent the F_1 population for further mating. Another male and female from each litter (if possible) were retained for organ weight measurement and tissue preservation. All other pups were sacrificed and examined grossly.

Shortly after weaning their F_{1B} pups, the F_0 rats were sacrificed and examined grossly. The reproductive organs of males which mated unsuccessfully were weighed and examined histopathologically. The uteri of all nonpregnant females were preserved. Tissues were weighed and examined histopathologically as described in the preceding table.

The F_{1B} rats were dosed with formulated feed for 13 weeks, then mated over a 20 day period, avoiding sibling unions. The dams reared their F_{2A} pups for 4 days before the litters were culled to 8 pups (4 pups/sex if possible). Unneeded pups were examined grossly. After 21 days of lactation, all surviving F_{2A} pups were sacrificed, examined grossly, and discarded. One male and 1 female from each litter (if possible) were retained for organ weight measurement and tissue preservation.

Ten days after the F_{2A} pups were weaned, the F_1 population was again mated over a 20 day period, avoiding sibling unions. The dams reared their F_{2B} pups for 4 days before the litters were culled to 8 pups (4 pups/sex if possible). Unneeded pups were examined grossly.

Beginning on lactation day 21, 1 male and 1 female F_{2B} pup per litter (if possible) were placed on the formulated diet for 13 weeks. At the end of this period, they were sacrificed. Their organs were weighed, and their tissues preserved. The other F_{2B} pups were sacrificed and examined grossly.

The F_{1B} parents were sacrificed shortly after weaning their second litters, and examined grossly. The reproductive organs of males which mated unsuccessfully were weighed and examined histopathologically. All nonpregnant females were examined by the Salewski technique (1964; ammonium sulphide was used to reveal implantation), and their uteri were preserved. Tissues were weighed and examined histopathologically as described in the above table.

All rats were regularly observed for clinical signs. Food consumption was measured weekly during the pre-mating phases of each generation. Body weight for the F_0 generation was measured one week prior to dosing and weekly thereafter. Females were also weighed on alternate days during mating, on gestation days 0, 7, 14, 17, and 20, and lactation days 0, 7, 14, and 21. All pups were weighed on lactation days 1, 4, 8, 12, and 21, and weekly thereafter if retained on study after weaning. All animals which died or were sacrificed moribund were examined grossly, and their tissues preserved.

The litters were counted, sexed, weighed, and examined for external lesions. Whenever abnormalities were suspected, the pups were histologically prepared for visceral or skeletal examination.

RESULTS: Dose concentration generally ranged between -14.7% and +8.8% of nominal, but it dipped to -22.0% of nominal in the low-dose group during week 59. The diet formulations were not adjusted to compensate for growth. Consequently, mean daily dosage decreased 60% in males and 50% in females as body weight increased. Because the F_0 animals were initially older than the other generations when their dosing commenced, their mg/kg/day doses were lower. The doses for all generations and mean doses were as follows:

Dose (ppm)	F_0 Male	F_0 Female	F_{1A} Male	F_{1A} Female	F_{1B} Male	F_{1B} Female	F_{2B} Male	F_{2B} Female	<< Mean >> Male	<< Mean >> Female
	---------- Dose (mg/kg/day) ----------									
0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
40	2.6	3.1	3.1	3.5	3.1	3.5	3.1	3.6	3.0	3.4
120	7.8	9.1	9.3	10.2	9.2	10.3	9.3	10.7	8.9	10.1
360	23.3	27.7	28.5	32.3	28.4	34.7	27.4	33.1	26.9	32.0

Parents: One low-dose and 3 mid-dose males died; and 1 control, 3 low-dose, 2 mid-dose, and 18 high-dose females died. The deaths in the high and mid-dose females could be attributed to the test article, and death was typically preceded by body tremors. Ten of the 18 high-dose female deaths occurred during lactation in the F_{1B} dams. Clinical signs observed in the high-dose dams of all generations included body tremors with spasmodic muscle twitches, and increased sensitivity. These signs were most frequent during the second and third weeks of lactation. One mid-dose F_{1B} dam also had these signs (during the second week of lactation). The low-dose and control dams had no compound-related clinical signs. No clinical signs were reported for the males; it is not clear whether or not the males were observed.

The mating indices, pregnancy rates, gestation length, and live births for the dosed F_0 and F_{1B} rats were similar to, or better than the controls. Organ weight anomalies included increased absolute and relative thyroid weights in the high-dose F_0 males, and decreased absolute and relative thyroid (all dosed groups) and pituitary (mid and high-dose) weights in F_{1B} males. All other adult F_0, F_{1B}, and F_2B groups had organ weights within normal limits. The histopathology data were not fully evaluable. There were no corresponding thyroid or pituitary lesions found, so the significance of these findings is doubtful.

Pups: Litter data for the F_{1A} pups was similar for all dosed and control groups. The high-dose F_{1B} pups had significantly decreased mean weight on lactation days 8, 12, and 21. The high-dose F_{2A} pups had increased loss (compared to controls) at lactation days 1, 4, 8, 12, and 21, but there was little overall effect in the mean litter size on lactation day 21. The high-dose F_2B pups had increased loss (compared to controls) at lactation days 4 and 21. There was no compound-related effect on the sex ratios. At 120 ppm, body tremors were observed in three F_{2B} pups, two of which subsequently died. Toxicology Branch considers these effects to be attributable to the test article.

Organ weight anomalies in the weanlings included increased absolute and relative pituitary weights in the F_{1A} males (high-dose) and females (mid and high-dose). There were absolute decreases in heart, liver, spleen, and kidney weights in the high-dose F_{1B} males and females which were due primarily to body weight loss. The female weanlings had significant increases in absolute and relative thyroid weights in the mid and high-dose groups. The thyroid weights were decreased in the F_{2A} male (all dose groups) and female (high-dose group) weanlings. Organ weights in the F_{2B} weanlings were within normal limits. As with the adults, the significance of the conflicting organ weight anomalies is doubtful; there were no corresponding histopathologic lesions found. The histopathology data for the F_{2B} weanlings were not fully evaluable, but there did not appear to be any compound-related lesions found.

40

Reviewed by: John E. Whalan JW 8-22-88
Section II, Tox. Branch (TS-769C)
Secondary reviewer: Edwin R. Budd Budd 8/22/88
Section II, Tox. Branch (TS-769C)
Tertiary reviewer: Kerry Dearfield Kerry Dearfield 8.25.88
SMSS, Tox. Branch (TS-769C)

84-2

006918

DATA EVALUATION REPORT

STUDY TYPE: Gene Mutation Test in Salmonella and E. Coli

ACCESSION NUMBER: 265391

TOX. CHEM. NO.: 273H

TEST MATERIAL: S-3206

MRID NO.: N/A

SYNONYMS: Fenpropathrin

STUDY NUMBER(S): FT-40-0107 and Addendum

SPONSOR: Sumitomo Chemical America, Inc.

TESTING FACILITY: Sumitomo Chemical Co., Ltd.

TITLE OF REPORT: Gene Mutation Test of S-3206 in Bacterial System

AUTHOR(S): Haruhi Izumozaki, Masaki Hara, and Takashi Suzuki

REPORT ISSUED: March 19, 1984

CONCLUSIONS: This study was negative for gene mutation in the bacteria strains tested.

STUDY CLASSIFICATION: This study is ACCEPTABLE. The study and the addendum received Quality Assurance review.

Special Review Criteria (40 CFR 154.7): N/A

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PROTOCOL: This study was performed using the methods of Ames et al. (1975), and Yahagi et al. (1975). The bacterial strains used included Salmonella typhimurium TA98, TA100, TA1535, TA1537, and TA1538 (his^-); and Escherichia coli WP2uvrA (trp^-). S-9 mix was obtained from the PCB activated livers of male Sprague Dawley rats. S-3206 (fenpropathrin, 92.5% pure) was dissolved in DMSO to yield dilutions of 0 (vehicle control), 50, 100, 500, 1000, and 5000 ug/plate. Volumes of 0.1 ml of the test article, and 0.1 ml of indicator cell suspension were mixed with either 0.5 ml of 100 mM sodium phosphate buffer (nonactivated systems), or 0.5 ml of S-9 mix (activated systems). These mixtures were incubated and agitated at 37° C for 20 minutes, then mixed with soft melted agar containing 0.05 mM histidine, and 0.05 mM biotin (for Salmonella strains), or 0.05 mM tryptophan (for E. Coli strains). These mixtures were cultured on minimal agar plates for 2 days at 37° C, after which revertant colonies were counted using a Biotran III automatic colony counter.

Two plates were used for each strain. The study was performed in duplicate using the Salmonella strains, but only once for E. coli. The positive control articles, methyl methanesulfonate (MMS), 2-nitrofluorene (2NF), 9-aminoacridine

(9AC), N-ethyl-N'-nitro-N-nitrosoguanidine (ENNG), 9-aminoanthracene (2AA), and benzo(A)pyrene (B(a)P), were used according to the following regimen:

Strain	<<<<<<<<<< Positive Control >>>>>>>>>>	
	Nonactivated Systems	Activated Systems
TA98	2NF	B(a)P
TA100	MMS	B(a)P
TA1535	ENNG	2AA
TA1537	9AC	B(a)P
TA1538	2NF	B(a)P
WP2uvrA	ENNG	2AA

RESULTS: The number of revertant colonies in the plates treated with the positive controls were increased 2.1 to 295-fold, thus demonstrating the sensitivity of the assay. There was a slight increase in revertant colonies in the nonactivated TA100 plates in one experiment, but since these results were not reproducible, they cannot be defined as a mutagenic effect. Thus, there was no evidence of mutagenicity in any of the nonactivated or activated plates treated with the test article. Some precipitation was observed at the 5000 ug/plate dose. Some higher doses were used, but there was no mention of what the doses were, or what was observed. This study was negative for gene mutation in the bacteria strains tested.

Reviewed by: John E. Whalan JW 8-22-88
Section II, Tox. Branch (TS-769C)
Secondary reviewer: Edwin R. Budd
Section II, Tox. Branch (TS-769C)
Tertiary reviewer: Kerry Dearfield
SMSS, Tox. Branch (TS-769C)

84-2

006918

DATA EVALUATION REPORT

STUDY TYPE: In Vitro Chromosome Aberration Study in Chinese Hamster Ovary Cells

ACCESSION NUMBER: 265391

TOX. CHEM. NO.: 273H

TEST MATERIAL: S-3206

MRID NO.: N/A

SYNONYMS: Fenpropathrin

STUDY NUMBER(S): FT-41-0104

SPONSOR: Sumitomo Chemical America, Inc.

TESTING FACILITY: Roma Toxicology Centre

TITLE OF REPORT: Chromosome Aberrations in Chinese Hamster Ovary (CHO) Cells In Vitro

AUTHOR(S): T. McSheehy and A. Nunziata

REPORT ISSUED: November 1, 1984

CONCLUSIONS: There was no evidence of test article-induced clastogenic effect at doses capable of reducing the mitotic index.

STUDY CLASSIFICATION: This study is UNACCEPTABLE. The materials and methods section was meager. The study design had to be gleaned from the summary and a general laboratory protocol which lacked information specific to this study. According to the study protocol, "...the highest dose for the main assay is fixed at a dose which produces approximately 50% inhibition of the mitotic index compared with the controls." The highest dose selected for the nonactivated system (500 ug/ml) not only did not inhibit the mitotic index, but was in fact 136% of the control value. There was no mention of the species source of the S-9 fraction. This study did not receive Quality Assurance Review.

Special Review Criteria (40 CFR 154.7): N/A

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PROTOCOL: This study was performed in two parts, a preliminary toxicity test, and the main cytogenetic test. A S-9 mix of unknown origin was used in both portions for metabolic activation. The test article was S-3206 (fenpropathrin, 92.5% pure), and the vehicle was DMSO.

The purpose of the Preliminary Toxicity Test was to establish concentrations to be used in the cytogenetic test. Chinese hamster ovary cells were treated at doses of 0 (vehicle control), 5, 15.8, 50, 158, 500, 1580, and 5000 ug/ml. Cyclophosphamide was used as the positive control at a concentration of 26.3 ug/ml. After 24 hours, the cells in the nonactivated system were fixed and mounted on slides for evaluation of the mitotic index. The cells in the

activated system were treated for 3 hours, after which they were washed twice with Ham's F10 medium and incubated for 30 minutes. They were then washed with Ham's F10 medium supplemented with 15% newborn calf serum, and incubated for 20.5 hours. The cells were then fixed and mounted on slides for evaluation of the mitotic index. Colchicine was not used in this portion of the study. The dose which resulted in approximately 50% inhibition of the mitotic index was selected as the maximum dose.

The doses used in the Main Cytogenetic Test were 0 (untreated control), 0 (vehicle control), 50, 158, and 500 ul/ml in the nonactivated system; and 0 (untreated control), 0 (venicle control), 500, 1580, and 5000 ul/ml. The positive control materials were mitomycin-C (0.3 ug/ml, in the nonactivated systems) and cyclophosphamide (13.15 ug/ml in the activated systems).

Flasks were seeded with 3 x 10^4 cells/ml in 10 ml of supplemented Ham's F10 medium. The medium was aspirated from the flasks and the cells washed with Hank's solution. In the nonactivated systems, treatment media consisting of 0.05 ml of the test article, positive control article, or vehicle control article and 4.95 ml of supplemented Ham's F10 medium was added to the flasks and incubated for 21 hours. Colchicine was then added, and the cultures were allowed to incubate for another 3 hours.

In the activated systems, treatment media consisting of 0.05 ml of the test article, positive control article, or vehicle control article; 0.5 ml of the S-9 mix; and 4.45 ml of supplemented Ham's F10 medium was added to the flasks and incubated for 3 hours. The medium was then aspirated, and the flasks were washed three times with calcium/magnesium free phosphate buffered saline. Fresh medium was added to the flasks, and the cultures were incubated for a 21 hour "recovery period." Colchicine was then added, and the cultures were allowed to incubate for another 3 hours.

The cells were harvested and mounted on slides for metaphase analysis and determination of a mitotic index (the percentage of cells in metaphase).

RESULTS: In the Preliminary Toxicity Test, the mitotic index was reduced in the nonactivated systems at doses of 1580 ug/ml (0.35%) and 5000 ug/ml (0.35%), and in the activated systems at the 5000 ug/ml dose (0.75%). Cyclophosphamide affected the mitotic index in the activated system (0.19%), but not in the nonactivated system due to the effects of metabolic activation. The maximum doses selected for the main cytogenetic test were 500 ug/ml for the nonactivated system, and 5000 ug/ml for the activated system.

In the Main Cytogenetic Test, the positive controls articles (mitomycin-C and cyclophosphamide) caused significant increases in defective cells, chromosomes, and chromatids, but there was no evidence of test article-induced clastogenic effect at doses capable of reducing the mitotic index.

Reviewed by: John E. Whalan
Section II, Tox. Branch (TS-769C)
Secondary reviewer: Edwin R. Budd
Section II, Tox. Branch (TS-769C)
Tertiary reviewer: Kerry Dearfield
SMSS, Tox. Branch (TS-769C)

JW 8-22-88
Budd 9/12/88
Kerry Dearfield 8.25.88

84-2

006918

DATA EVALUATION REPORT

STUDY TYPE: Micronucleus Test in Mice

ACCESSION NUMBER: 265391

TOX. CHEM. NO.: 273H

TEST MATERIAL: S-3206

MRID NO.: N/A

SYNONYMS: Fenpropathrin

STUDY NUMBER(S): FT-40-0106 and Addendum

SPONSOR: Sumitomo C[illegible] America, Inc.

TESTING FACILITY: Sumitomo Chemical Co., Ltd.

TITLE OF REPORT: Micronucleus Test of S-3206

AUTHOR(S): Masaki Hara and Tekashi Suzuki

REPORT ISSUED: March 19, 1984

CONCLUSIONS: There were no mutagenic effects caused by either S-3206 or the vehicle control (corn oil) in either the dose-response or time course studies.

STUDY CLASSIFICATION: This study is UNACCEPTABLE. Only male mice were used. In the absence of information regarding sex differences, both sexes should have been used. There was no evidence that S-3206 or the corn oil vehicle reached the bone marrow in sufficient concentration to potentially elicit a response, but under the conditions of this study, the results were negative. This study and the Addendum received Quality Assurance review.

Special Review Criteria (40 CFR 154.7): N/A

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PROTOCOL: Groups of 6 male ICR mice (32-39 g, 7-8 weeks old) were dosed intraperitoneally with S-3206 (fenpropathrin, 92.5% pure) dissolved in corn oil at doses of 0 (vehicle control), 50, 100, and 200 mg/kg. Positive control groups were dosed with 2 mg/kg of Mitomycin C in saline. All dose volumes were 10 ml/kg. The following dosing regimens were used:

	Test Article	Dose (mg/kg)	Sacrifice Interval (hr)
Experiment 1			
	Corn Oil	0	24
	S-3206	50	24
	S-3206	100	24
	S-3206	200	24
	Mitomycin C	2	24

45

Experiment 2	Corn Oil	0	24
	S-3206	200	24
	S-3206	200	48
	S-3206	200	72
	Mitomycin C	2	24

Experiment 1 was designed to assess dose-related effects, and Experiment 2 was designed to assess the effect of one dose (200 mg/kg) over time. The mice were sacrificed by cervical dislocation. Their femurs were removed and the marrow aspirated with 0.3 ml of fetal bovine serum. The marrow cells were centrifuged, and the packed cells were suspended in residual serum in order to make smears. The smears were fixed and stained (5% Giemsa in phosphate buffer), and analyzed for the occurrence of micronucleated erythrocytes (RBC's having darkly stained, sharply outlined particles) per 1000 whole erythrocytes and the occurrence of micronucleated cells per 1000 polychromatic erythrocytes.

RESULTS: The positive control article (mitomycin C) caused a decrease in polychromatic and micronucleated erythrocytes in the marrow 24 hours after dosing. There were no corresponding mutagenic effects caused by either S-3206 or the vehicle control (corn oil) in either the dose-response or time course studies.

Reviewed by: John E. Whalan JW 8-22-88
Section II, Tox. Branch (TS-769C)
Secondary reviewer: Edwin R. Budd
Section II, Tox. Branch (TS-769C)
Tertiary reviewer: Kerry Dearfield
SMSS, Tox. Branch (TS-769C)

84-2

006918

DATA EVALUATION REPORT

STUDY TYPE: In Vitro Sister Chromatid Exchange Test in CHO-K1 Cells

ACCESSION NUMBER: 265391

TOX. CHEM. NO.: 273H

TEST MATERIAL: S-3206

MRID NO.: N/A

SYNONYMS: Fenpropathrin

STUDY NUMBER(S): FT-40-0108 and Addendum

SPONSOR: Sumitomo Chemical America, Inc.

TESTING FACILITY: Sumitomo Chemical Co., Ltd.

TITLE OF REPORT: In Vitro Sister Chromatid Exchange Test of S-3206 in CHO-K1 Cells

AUTHOR(S): Masaki Hara and Takashi Suzuki

REPORT ISSUED: March 19, 1984

CONCLUSIONS: There was no increase in sister chromatid exchanges seen in the cells treated with S-3206 or the DMSO vehicle.

STUDY CLASSIFICATION: This study is ACCEPTABLE. The study and the addendum received Quality Assurance review.

Special Review Criteria (40 CFR 154.7): N/A

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PROTOCOL: The test articles used in this study were DMSO as the vehicle, S-3206 (fenpropathrin, 92.5% pure) dissolved in DMSO at concentrations of 3×10^{-6}, 1×10^{-5}, 3×10^{-5}, and 1×10^{-4} M (the limit of solubility), mitomycin C in saline at a concentration of 1×10^{-7} M, and cyclophosphamide in saline at a concentration of 5×10^{-6} M. Mitomycin C was the positive control article for the nonactivated system, and cyclophosphamide was the positive control article for the activated system.

Chinese hamster ovary K1 cells were cultured for 24 hours in Ham's F12 medium supplemented with 10% fetal bovine serum, penicillin, streptomycin, and fungizone in a 5% CO_2 atmosphere with a temperature of 37° C. The medium was then decanted and the cells were washed with Ham's F12 medium without serum.

The cells in the nonactivated system were dosed with 0.5 ml of the test articles and 5 ml of medium without serum. The S-9 mix was obtained from the PCB activated livers of male Sprague Dawley rats. The cells in the activated system were dosed with 0.5 ml of S-3206, 0.5 ml of S-9 mix, and 4.5 ml of medium without serum.

#7

Two hours later, the cells were washed and cultured for another 28 hours in complete medium supplemented with 3 uM of 5-bromodeoxyuridine. The cells were dosed for the last two hours with 0.1 ug/ml of Colcemid. Trypsinization was used to harvest the cells. They were centrifuged, treated with KCl, fixed, and mounted onto glass slides. Staining was by the method of Perry and Wolff (1974). Fifty metaphases per treatment were counted for sister chromatid exchange. The experiment was run in duplicate.

RESULTS: The positive control articles both had significantly increased incidences of sister chromatid exchange and reduced numbers of cells in metaphase. There was no increase in sister chromatid exchanges seen in the cells treated with S-3206 or the DMSO vehicle.

48

Reviewed by: John E. Whalan JW 8-1-88
Section II, Tox. Branch (TS-769C)
Secondary reviewer: Edwin R. Budd Budd 9/12/88
Section II, Tox. Branch (TS-769C)
Tertiary reviewer: Robert Zendzian
Senior Pharmacologist, Tox. Branch (TS-769C)

85-3

206915

DATA EVALUATION REPORT

STUDY TYPE: Percutaneous Absorption in Rats

ACCESSION NUMBER: 265392

TOX. CHEM. NO.: 273H

TEST MATERIAL: SX-1491

MRID NO.: N/A

SYNONYMS: Fenpropathrin

STUDY NUMBER(S): SOCAL 2208

SPONSOR: Sumitomo Chemical America, Inc.

TESTING FACILITY: Chevron Environmental Health Center, Inc.

TITLE OF REPORT: The Percutaneous Absorption of Fenpropathrin Technical in Adult Male Rats

AUTHOR(S): Y.S. Chen, J. Abell, A.A. Carey, C.M.. Cisson, and Z.A. Wong

REPORT ISSUED: April 17, 1985

CONCLUSIONS: Over a 24 hour period, very little fenpropathrin was absorbed through the skin. The major route of elimination was the urine.

STUDY CLASSIFICATION: This study is UNACCEPTABLE. The dosing sites were probably not adequately protected. Rats No. 245, 434, 447, and 457 had excessively high levels of carcass residue, presumably due to ingestion of the test article. The latter three (434, 447, and 457) were not properly restrained. The dosing sites should have been washed with soap and water in order to mimic dose removal by dermally exposed pesticide applicators. The materials and methods describe the high-dose rats being sacrificed at intervals of 0, 2, 4, and 24 hours, but all other tables and text in the report mention intervals of 0, 2, 8, and 24 hours (the same as for the low-dose group). The latter is assumed to be correct. It is preferrable to test the end-use product instead of the technical. A suggested protocol is attached. This study received Quality Assurance review.

Special Review Criteria (40 CFR 154.7): N/A

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PROTOCOL: Dosing suspensions were prepared by combining ^{14}-C-fenpropathrin (>99% pure) and unlabelled SX-1491 (fenpropathrin, 90.3% pure) in distilled water, 0.5% (w/w) Tween 80, and 1.0% (w/w) carboxymethyl cellulose. Groups of 16 male Sprague-Dawley Crl:CD(SD)BR rats (451-538 g; 96-98 days old) were given dermal doses of 0.5 mg/rat (5 mg/ml; 4 uCi/mg) or 5.0 mg/rat (50 mg/ml; 0.4 uCi/mg). Four rats/group were sacrificed 0, 2, 8, and 24 hours (low-dose) and 0, 2, 4, and 24 hours (high-dose) after being dosed. They were dosed on the intact skin of the back after being shaved and cleaned with soap and water.

#9

The sites were approximately 2.1% of the body surface area [calculated by the equation: $A = 9.64 \times (\text{body weight})^{0.66}$]. The dosing volume was 0.10 ml. The rats scheduled for immediate sacrifice were anesthetized with sodium pentobarbital. The dosed skin was removed from the animal's backs, and washed with acetone and methanol/water. Samples of arterial blood were drawn from the descending aorta prior to exsanguinating the animals. Strips of undosed skin and the carcasses were retained. The rats sacrificed at the other intervals were treated similarly, except that samples of urine in the bladder and cage were weighed, and all feces from the colon, cecum, and cage were collected. The metabolism cages in which they had been housed were washed with methanol, and the residue was retained. All samples of blood, skin, urine, feces, carcasses, and cage washings were measured for radioactivity. All sampled materials and surfaces were measured for radioactivity. Photocopied data tables are attached.

RESULTS: The mean doses were 0.507 mg/rat (1.035 mg/kg) and 5.171 mg/rat (10.758 mg/kg), respectively for the low and high-dose groups. Total dose recovery (based on radioactivity measurements) ranged from 92.5 to 108.8% for the low-dose, and from 61.1 to 120.3% for the high-dose. Most of the administered doses were recovered from the surface of the skin, with lesser recovery from skin residue:

	Recovery From Skin Surface (%)			
Dose (mg/kg)	0 Hr	2 Hr	8 Hr	24 Hr
0.5	97.7	92.8	84.7	82.8
5.0	99.3	96.7	90.5	78.8

	Recovery From Skin Residue (%)			
Dose (mg/kg)	0 Hr	2 Hr	8 Hr	24 Hr
0.5	0.6	5.1	8.3	9.3
5.0	0.1	0.7	0.8	1.1

Recovery in the blood was <0.1% for all groups. Over time, dose recovery decreased on the skin surface, and increased in the skin residue, urine, feces, and carcass. After 24 hours, recovery levels in the low and high-dose groups respectively reached 2.8% and 0.8% in the urine, 0.4% and 1.5% in the feces, and 2.8% and 6.1% in the carcass. These data demonstrate that over a 24 hour period, very little fenpropathrin was absorbed through the skin. The major route of elimination was the urine.

50

PERCUTANEOUS ABSORPTION OF FENPROPATHRIN TECHNICAL
IN ADULT MALE RATS

TABLE 5

TOTAL RECOVERY OF ^{14}C-FENPROPATHRIN EQUIVALENT

(% OF ADMINISTERED DOSE)

0.5 MG/RAT

Time After Dosing (Hr)	Animal No.	Acetone Skin Wash	MeOH: Water Skin Wash	Skin Residue	MeOH Template Wash	Blood	Urine	Feces	Carcass	MeOH Cage Wash	Total
0	401	98.8	1.0	0.9	0.3	<0.1	NE	NE	NE	NE	101.0
	441	104.1	0.4	0.1	0.2	<0.1	NE	NE	NE	NE	104.8
	469	100.2	0.7	0.5	0.4	<0.1	NE	NE	NE	NE	101.8
	228	97.7	3.0	0.9	0.9	<0.1	NE	NE	NE	NE	102.5
										Mean	102.5
										S.D.	1.6
2	452	97.5	2.3	4.2	0.1	<0.1	<0.1	<0.1	0.2	<0.1	104.2
	313	94.2	1.3	8.7	0.1	<0.1	<0.1	<0.1	0.3	<0.1	104.5
	420	95.3	1.6	6.7	0.1	<0.1	<0.1	<0.1	0.3	<0.1	104.0
	466	104.1	2.7	1.9	0.1	<0.1	<0.1	<0.1	0.1	<0.1	108.8
										Mean	105.4
										S.D.	2.3
8	486	79.1	2.4	11.1	0.1	<0.1	0.3	<0.1	1.5	0.3	94.8
	473	78.1	2.2	10.1	0.2	<0.1	0.2	<0.1	0.9	0.8	92.5
	33	83.6	8.5	5.2	0.1	<0.1	0.3	<0.1	0.8	<0.1	98.4
	424	86.1	7.0	5.3	0.1	<0.1	0.2	<0.1	1.6	<0.1	100.3
										Mean	96.5
										S.D.	3.5
24	58	86.9	2.0	9.3	0.1	<0.1	2.9	0.3	2.2	0.1	103.7
	87	79.8	1.4	7.9	0.6	0.1	4.6	0.7	5.3	0.6	101.0
	402	85.7	1.4	14.0	0.1	<0.1	2.0	0.4	2.2	0.1	105.8
	465	90.0	1.1	7.4	0.1	<0.1	1.9	0.1	2.0	0.4	103.0
										Mean	103.4
										S.D.	2.0

NE = not examined.

51

CMC:vll/mnb-22b
s2208tbls
4-3-85

006918

PERCUTANEOUS ABSORPTION OF FENPROPATHRIN TECHNICAL
IN ADULT MALE RATS

TABLE 6

TOTAL RECOVERY OF ^{14}C-FENPROPATHRIN EQUIVALENT

(% OF ADMINISTERED DOSE)

5.0 MG/RAT

Time After Dosing (Hr)	Animal No.	Acteone Skin Wash	MeOH: Water Skin Wash	Skin Residue	MEOH Template Wash	Blood	Urine	Feces	Carcass	MEOH Cage Wash	Total
0	461	113.7	0.5	0.1	0.3	<0.1	NE	NE	NE	NE	114.6
	147	107.9	0.3	0.1	<0.1	<0.1	NE	NE	NE	NE	108.3
	437	119.4	0.7	0.2	<0.1	<0.1	NE	NE	NE	NE	120.3
	474	110.5	0.2	0.1	0.6	<0.1	NE	NE	NE	NE	111.4
										Mean	113.7
										S.D.	5.1
2	180	96.4	0.5	0.6	1.0	<0.1	<0.1	<0.1	0.6	<0.1	99.1
	332	99.0	0.1	0.6	<0.1	<0.1	<0.1	<0.1	4.8	<0.1	104.5
	490	110.3	1.5	1.2	<0.1	<0.1	<0.1	<0.1	0.5	<0.1	113.5
	450	101.0	0.3	0.4	0.4	<0.1	<0.1	<0.1	1.5	<0.1	103.6
										Mean	105.2
										S.D.	6.0
3	245	43.1	0.6	0.4	14.0	<0.1	0.1	<0.1	2.5	0.4	61.1
	448	104.0	0.5	0.5	0.5	<0.1	<0.1	0.1	0.8	0.1	106.5
	451	105.7	0.7	1.4	<0.1	<0.1	0.1	<0.1	0.4	<0.1	108.3
	421	100.4	0.4	0.6	2.5	<0.1	<0.1	<0.1	0.6	<0.1	104.5
										Mean	95.1
										S.D.	22.7
24	434	70.0	0.2	1.4	5.0	<0.1	0.4	0.2	1.7	8.5	87.4
	104	103.2	0.3	0.8	<0.1	<0.1	0.3	<0.1	0.6	0.1	105.3
	457	71.5	0.2	0.8	1.9	<0.1	0.7	2.3	5.7	1.2	84.3
	447	37.8	0.2	0.9	16.0	<0.1	1.0	2.1	11.0	3.2	72.2
										Mean	87.3
										S.D.	13.7

NE = not examined.

52

CMC:vll/mnb-22b
s2208tbls
4-3-85

006918

PERCUTANEOUS ABSORPTION OF FENPROPATHRIN TECHNICAL
IN ADULT MALE RATS

TABLE 7

MEAN NORMALIZED RECOVERY OF ^{14}C-FENPROPATHRIN EQUIVALENT

(% OF RECOVERED DOSE)

0.5 MG/RAT

Time After Dosing (Hr)		Acetone Skin Wash	MeOH: Water Skin Wash	Skin Residue	MeOH Template Wash	Blood	Urine	Feces	Carcass	MeOH Cage Wash
0	Mean	97.7	1.3	0.6	0.5	<0.1	NE	NE	NE	NE
	S.D.	1.7	1.1	0.4	0.3	-	-	-	-	-
	N	4	4	4	4	4	-	-	-	-
2	Mean	92.8	1.9	5.1	<0.1	<0.1	<0.1	<0.1	0.2	<0.1
	S.D.	2.4	0.6	2.9	-	-	-	-	0.1	-
	N	4	4	4	4	4	4	4	4	4
8	Mean	84.7	5.1	8.3	0.1	<0.1	0.3	<0.1	1.3	0.3
	S.D.	1.0	3.2	3.5	0.1	-	0.1	-	0.4	0.4
	N	4	4	4	4	4	4	4	4	4
24	Mean	82.8	1.4	9.3	0.2	<0.1	2.8	0.4	2.8	0.3
	S.D.	3.6	0.3	2.7	0.3	-	1.3	0.3	1.6	0.2
	N	4	4	4	4	4	4	4	4	4

NE = not examined.

CMC:v11/mnb-22b
s2208tbls
4-3-85

PERCUTANEOUS ABSORPTION OF FENPROPATHRIN TECHNICAL
IN ADULT MALE RATS

TABLE 8

MEAN NORMALIZED RECOVERY OF ^{14}C-FENPROPATHRIN EQUIVALENT

(% OF RECOVERED DOSE)

5.0 MG/RAT

Time After Dosing (Hr)		Acetone Skin Wash	MeOH: Water Skin Wash	Skin Residue	MeOH Template Wash	Blood	Urine	Feces	Carcass	MeOH Cage Wash
0	Mean	99.3	0.4	0.1	0.2	<0.1	NE	NE	NE	NE
	S.D.	0.2	0.2	0.1	0.2	-	-	-	-	-
	N	4	4	4	4	4	-	-	-	-
2	Mean	96.7	0.6	0.7	0.4	<0.1	<0.1	<0.1	1.8	<0
	S.D.	1.3	0.5	0.3	0.5	-	-	-	2.0	-
	N	4	4	4	4	4	4	4	4	4
8	Mean	90.5	0.6	0.8	6.5	<0.1	0.1	<0.1	1.5	0.2
	S.D.	13.3	0.3	0.4	11.0	-	0.1	-	1.8	0.3
	N	4	4	4	4	4	4	4	4	4
24	Mean	78.8	0.3	1.1	7.6	<0.1	0.8	1.5	6.1	3.9
	S.D.	19.2	0.1	0.4	10.0	-	0.5	1.6	6.6	4.3
	N	4	4	4	4	4	4	4	4	4

NE = not examined.

CMC:vll/mnb-22b
s2208tbls
4-3-85

Procedure for Studying Dermal Absorption

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Introduction

This paper presents a general procedure for dermal absorption studies on pesticides which is applicable to any compound or formulation of a compound. The study requires application of various doses of radiolabeled compound to the shaven skin of male rats followed, at specific intervals after dosing, by total urine and fecal collection, determination of blood concentration, determination of the quantity in the body and determination of the quantity remaining on the skin. It is assumed that a metabolism study of the test compound has been performed in the rat before the dermal absorption study is undertaken.

The rat is used for purely practical reasons, it is not intended as a model of absorption through the human skin but rather as a test system for dermal absorption. The domestic rat is a conveniently sized animal, which is readily available and used for most of the toxicology studies on pesticides including metabolism. Because of its small size, several animals can be used per dose and several dose levels per compound within the constraints of time and resorces. Foreign compounds in general pass more rapidly through rat skin than through human skin and thus determination of dermal penetration in the rat offers a built-in safety factor for projection to human exposure.

The study described here combines two different types of dermal absorption studies in a manner which can compensate for their individual deficiencies and simultaneously cover the full range of possible dermal absorption patterns. The first type of study involves placing a measured quantity of compound on the skin for a specific period of time. The animal is then killed and the treated skin is removed. The quantity remaining on the skin is determined and the quantity of compound absorbed is calculated by subtraction. This method works very well for small quantities of a compound which does not fall or vaporize off of the skin. Large quantities, volatile compounds or strange solvents, cannot be used in this procedure.

The second type of study measures what goes into the animal. The compound is applied to the skin in a measured dose and the quantity in the body and the quantity excreted for a specific time period is measured. The procedure has greater possibilities for error in very low doses, for compounds which are not rapidly excreted and for compounds which are completely metabolized to CO_2, water and urea.

Materials

Twenty-four young adult male rats, 225-250 grams in weight, are used at each dose point. It is preferred that the rats be of the same strain used for metabolism studies on the test compound.

The compound should be chemically pure and radiolabeled, usually with carbon-14, in a position which is part of the "core" of the compound. The label should follow the compound and its major metabolites until excreted. The label should not be exchangeable nor should it be metabolically removed to CO_2 or become part of the one-carbon pool of the organism. Double labeling may sometimes be necessary. Unlabeled compound may be used if a sufficiently specific and sensitive test is available.

Methods

Twenty-four hours prior to dosing the back and shoulders of the rats are clipped free of hair and the area washed with acetone. Do not damage the skin.

Twenty-four animals are used per dose. A minimum of three but preferably four doses, at log intervals should be used. The doses should span the range of dose per unit area of skin which can be expected to occur in human exposure. Experience has shown that the highest useful dose is in the order of 10 mg/rat with descending doses of 1, 0.1, and 0.01 mg/rat. If less then four doses are used it is preferred that the lower dose range be used. Doses must be mass/unit area of skin (mg/cm^2) and not mass/body weight (mg/kg) since the rate of absorption is directly related to mass/unit area.

The compound is applied to a measured area of the rat's skin, at least 10 cm^2, in the form applied in the field utilizing the field solvent. Usually the use product (emulsifiable concentrate, flowable powder etc.) is used for the highest dose and is diulted with water for the lower doses. When no solvent is specified, as for the technical material or a dust, the compound is dissolved or suspended in water. Organic solvents should not be used. The material is spread evenly until dry. The spreader should be checked for loss of material. The treated area is covered with a nonocclusive cover to prevent loss by falling or being rubbed off and to prevent the animal eating the test material.

Experience has shown that the application area must be covered. A combination cover consisting of a 'spacer' glued to the skin and a filter paper or gauze glued to the ring appears to be most effective. The 'spacer' will outline the application site and be sufficiently thick to hold the cover from contact with the site.

The treated animals are placed individually in metabolism cages. All urine and feces are collected, a single collection for the entire duration of exposure. At intervals of 1/2, 1, 2, 4, 10 and 24 hours, four animals per dose are anesthetized. The exposed skin and residual compound are collected separately by washing the skin with a mild soap solution followed by several water rinses. Liquid Ivory or Dove for dishwashing is suggested. The skin must be washed before killing the animals, as up to three fold differences have been observed in the ability of skin on the live animal and skin from the killed animal to bind test compounds. The animals are killed, a blood sample taken, and residual urine collected from the bladder and added to the collected urine. Any material on the protective appliance is measured. The remainder of the animal is prepared for determination of the quantity of compound in the carcass.

For each animals the following determinations are made. Results are expressed as quantity or concentration of the parent compound and as percent of applied dose. Metabolites are not separately distinguished.

1) The quantity of the compound in/on the application device and the protective appliance.

2) The quantity of compound that can be washed from the skin.

3) Quantity of compound remaining on/in the skin at the application site which cannot be removed by washing.

4) Concentration of compound in the blood and from this the quantity of compound in the blood.

5) Quantity of compound excreted in the urine and feces.

6) Quantity of material remaining in the carcass.

Results and Conclusions

From the quantity determined in parts 1 and 2 above one may calculate, by subtraction the quantity absorbed provided that other routes of loss are not significant. Excessive variation of results within groups at the same time and dose will indicate external loss of the dose.

From the quantity in the skin, the quantity excreted, the quantity in the blood and the quantity remaining in the carcass one may obtain directly the quantity absorbed. The quantity which cannot be removed from the skin by washing is considered potentially able to be absorbed and, if the amount is large, special studies may be required to quantitate its potential for absorption.

The blood concentration of the compound can be used for a direct comparison with other studies on the compound.

Graphs relating dose, time and amount absorbed may be constructed and used to calculate absorption for doses which are not directly studied. Using proper assumptions one may extrapolate to estimate human absorption under conditions of normal exposure.

Additional procedures

1) Procedure to define compounds which are essentially not absorbed.

Results from a study of a compound expected to have little or no dermal absorption have suggested the necessity of treating an additional group of rats. In the study, analysis of the dermal residue indicated no absorption to a limit of 0.1 percent of the dose. This limit was defined by the variability of recovery of compound from the skin. The blood showed no radioactivity at any dose and duration of exposure. The urine showed radioactivity which did not appear to follow the dose and duration of exposure relationship expected. In only one of nine treatment groups were the results internally consistent with all four animals showing similar positive results. In the other eight groups the number of animals having radioactivity in the urine ranged from zero to three with a mean of 1.5. These results appeared indicative of contamination of the urine rather than dermal absorption.

Under such circumstances an additional group of four rats should be treated with the high dose at the 10 and 24 hour durations of exposure. These animals should have their urinary bladders cannulated to avoid contamination of the urine collected during the exposure period. Samples of blood, urine and carcass should be counted for the longest practical time in order to produce the lowest possible limit of dermal absorption. In the case where no absorption occurs under the experimental conditions the limit of dermal absorption will be defined solely by the sensitivity of the method for detecting the radio tracer.

2) Procedure for examining compounds which show a major residue on/in the washed skin.

Several compounds have been tested which show a significant residue on/in the skin despite vigorous washing. The concentration has appeared in short exposures and shows little or no increase with time and often does not appear to increase to any large extent with increase of dose. This suggests a binding process.

For regulatory purposes one must assume that this material is available for further absorption. However, this may not be true particularly in cases were little or no detectable compound appears in blood, excreta and/or carcass. However, studies such as the one suggested below have shown that absorption of the residue following washing can range from none detectable to essentially all, over a period of two weeks after dosing.

In such cases the following additional study is suggested.

1) Eight rats per dose are treated for the time period which shows the maximum skin concentration (or ten hours).

2) At the end of the exposure period 4 rats per dose are treated as in the basic protocol.

3) The skin of the remaining 4 rats per dose, is washed in the same fashion used in the basic study and the animals followed for at least an additional 72 hours. A study which carried the post-wash period for up to three weeks showed maximum absorption at two weeks. This appears to be a practical limit for observation.

4) The animals are then treated as in the basic protocol.

A balance comparison of the various residues will give some indication as to whether or not the quantity in the washed skin can be absorbed and quantitation of any absorption. If absorption occurs it may be necessary to repeat this process with longer post washed periods to obtain a quantitation of absorption over time.

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Please note. This procedure has been developed by the experimental work performed on pesticides by Registrants in their own or contract laboratories. Their continued work provides valuable and unique information on improving the experimental design and methodology. It is strongly advised that you contact the Agency before performing a dermal absorption study on a pesticide in order to take advantage of the most recent information. You may submit your protocol, through the Registration Division, for evaluation by the author of this document.

Reviewed by: John E. Whalan JW 8-22-88
Section II, Tox. Branch (TS-769C)
Secondary reviewer: Edwin R. Budd
Section II, Tox. Branch (TS-769C)

81-3

006918

DATA EVALUATION REPORT

STUDY TYPE: Acute Inhalation in Mice

ACCESSION NUMBER: 265370

TOX. CHEM. NO.: 273H

TEST MATERIAL: Danitol 2.4 EC (SX-1714)
Clear amber liquid

MRID NO.: N/A

SYNONYMS: Fenpropathrin

STUDY NUMBER(S): CEHC 2550

SPONSOR: Sumitomo Chemical America, Inc.

TESTING FACILITY: Chevron Environmental Health Center, Inc.

TITLE OF REPORT: The Acute Inhalation Toxicity of Danitol 2.4 EC (SX-1714) in Mice

AUTHOR(S): D.C. Gilley, L.C. Griffis, Z.A. Wong

REPORT ISSUED: September 4, 1986

CONCLUSIONS: The approximate LC_{50} values for diluted Danitol 2.4 EC are 4.3 mg/l for males and 4.5 mg/l for females. Dose-related clinical signs included eyes squinted or closed, tremors, elevated gait [sic] in the hindquarters, hindlimb muscle jerks, phonation, hunched posture, unkempt appearance, dyspnea, collapse, convulsions, and decreased body weights (females). There were no compound-related gross or histopathologic lesions. It is uncertain what effect the large amount of diluent may have had on the expression of toxicity.

STUDY CLASSIFICATION: This study is CORE SUPPLEMENTARY. Rather than dosing mice with Danitol 2.4 EC, an aqueous dilution (0.6% v/v) was used instead. This is contrary to the EPA Guidelines which stipulate that an acute inhalation study must be performed using the technical product, manufacturing-use product, or end-use product. No reason was given for using a dilution. The probit results summarized above are unreliable as demonstrated by the extremely wide confidence limits for both the LC_{50} values and slopes. In the case of the males, there was only one data point (the high-concentration) with which to plot a dose-response curve and calculate an LC_{50}.

Special Review Criteria (40 CFR 154.7): N/A

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PROTOCOL: Groups of 5 male (31.6-37.7 g) and 5 female (22.2-28.9 g) Swiss-Webster mice (Crl:CD-1(ICR)BR (56-73 days old) were dynamically exposed for 4 hours in a 0.42 m^3 stainless steel chamber to nominal concentrations of 0 (negative control), 16.3 (females only), 25.8, 47.0, and 47.0 mg/l of a 0.6% v/v aqueous dilution of Danitol 2.4 EC aerosol. The test article was formulated by dissolving 12 ml of the test article into 2 liters of distilled water. Aerosols were generated with an Ohio High Output Pneumatic Nebulizer.

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with a multijet cascade impactor. Atomsphere samples were collected near the breathing zone on Whatman GF/A filters; these were used to measure gravimetric concentrations. The mice were housed individually during exposure.

Body weights were measured prior to exposure, and on days 2, 7, and 14. The mice were observed for clinical signs at least once during and following the exposure. All survivors were sacrificed and examined grossly. Sections of lungs and tracheas were examined histopathologically. Food and water were available ad libitum except during exposure.

RESULTS: The nominal and analytical concentrations, MMAD values with geometric standard deviations, and mortality were as follows:

Concentration			MMAD (Gsd)	Mortality	
Nominal	Analytical			Male	Female
	Total	A.I.			
0 mg/l	0 mg/l	0 ug/l	—	—	—
16.3 mg/l	0.48 mg/l	5.9 ug/l	1.44 (2.31-2.40) um	—	0/5
25.8 mg/l	1.7 mg/l	9.8 ug/l	2.01 (2.64-3.47) um	0/5	1/5
47.0 mg/l	4.0 mg/l	12 ug/l	3.12 (4.21-4.10) um	0/5	1/5
47.0 mg/l	4.9 mg/l	13 ug/l	4.02 (4.27-4.92) um	4/5	4/5

A significant portion of the particles in the 0.48 and 1.7 mg/l concentrations were in the respirable range (≤1 um). The majority of particles in the 4.0 and 4.9 mg/l concentrations were not respirable, and were too large (i.e. >2 um) to avoid being captured in the nasal region.

The results of probit analyses for the active ingredient (by the method of Berkson) are tabulated below. Because the confidence limits are extremely wide, these values can only be considered approximate.

Total Diluted (Danitol 2.4 EC):

	LC_{50} (95% confidence limits)	Slope (95% confidence limits)
Male	4.3 (0.1-182.2) mg/l	1.9 (0.02-174.5)
Female	4.5 (0.3-73.7) mg/l	4.5 (0.1-197.1)
Combined	5.0 (0.7-34.5) mg/l	3.5 (2.7-39.5)

Active Ingredient:

	LC_{50} (95% confidence limits)	Slope (95% confidence limits)
Male	12.4 (5.4-28.5) ug/l	1.2 (0.5-2.9)
Female	12.9 (5.0-33.6) ug/l	1.7 (0.4-6.2)
Combined	13.3 (6.8-26.0) ug/l	1.5 (0.7-3.6)

Dose-related clinical signs included eyes squinted or closed, tremors, elevated gait [sic] in the hindquarters, hindlimb muscle jerks, phonation, hunched posture, unkempt appearance, dyspnea, collapse, and convulsions. Body weights were significantly reduced in 4.0 and 4.9 mg/l famales on day 2. It was impossible to tell if the sole surviving high-dose male was affected. There were no compound-related gross or histopathologic lesions.

Reviewed by: John E. Whalan JW 8-22-88
Section II, Tox. Branch (TS-769C)
Secondary reviewer: Edwin R. Budd
Section II, Tox. Branch (TS-769C) Budd 9/12/88

81-3

006918

DATA EVALUATION REPORT

STUDY TYPE: Acute Inhalation in Rats

ACCESSION NUMBER: 265371

TOX. CHEM. NO.: 273H

TEST MATERIAL: Danitol 2.4 EC (SX-1714)
Clear amber liquid (32.8% a.i.)

MRID NO.: N/A

SYNONYMS: Fenpropathrin

STUDY NUMBER(S): CEHC 2551

SPONSOR: Sumitomo Chemical America, Inc.

TESTING FACILITY: Chevron Environmental Health Center, Inc.

TITLE OF REPORT: The Acute Inhalation Toxicity of Danitol 2.4 EC (SX-1714) in Rats

AUTHOR(S): D.C. Gilley, L.C. Griffis, Z.A. Wong

REPORT ISSUED: September 5, 1986

CONCLUSIONS: The limit test was technically attained with a gravimetric concentration of 5.4 mg/l (13 ug a.i./l) being toxic, but not lethal. Clinical signs included salivation, red or colorless nasal discharge, squinted or closed eyes, tachypnea, tremors, ataxia, and wet muzzles and fur. All signs had reversed by day 2. There were no effects on body weight gain, and no compound-related gross or histopathologic lesions. It is uncertain what effect the large amount of diluent may have had on the expression of toxicity.

STUDY CLASSIFICATION: This study is CORE SUPPLEMENTARY. Rather than dosing rats with Danitol 2.4 EC, an aqueous dilution (0.6% v/v) was used instead. This is contrary to the EPA Guidelines which stipulate that an acute inhalation study must be performed using the technical product, manufacturing-use product, or end-use product. No justification was given for using such a weak dilution.

Special Review Criteria (40 CFR 154.7): N/A

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PROTOCOL: Groups of 5 male (270-284 g) and 5 female (186-197 g) Sprague-Dawley CD rats (52 days old) were dynamically exposed for 4 hours in a 0.42 m^3 stainless steel chamber to a nominal concentration of 0 (negative control) and 45.6 mg/l of a 0.6% v/v aqueous dilution of Danitol 2.4 EC aerosol. The test article was formulated by dissolving 12 ml of the test article into 2 liters of distilled water. Aerosols were generated with an Ohio High Output Pneumatic Nebulizer. Fresh suspensions were prepared every 30 minutes. Particle size was measured with a multijet cascade impactor. Atmosphere samples were collected near the breathing zone on Whatman GF/A filters; these were used to measure gravimetric concentrations. The rats were housed individually

during the exposure. Body weights were measured prior to exposure, and on days 2, 7, and 14. The mice were observed for clinical signs at least once during and following the exposure. All survivors were sacrificed and examined grossly. Sections of lungs and tracheas were examined histopathologically. Food and water were available ad libitum except during exposure.

RESULTS: The nominal and analytical concentrations, MMAD values with geometric standard deviations, and mortality were as follows:

Concentration			MMAD (Gsd)	Mortality	
Nominal	Analytical			Male	Female
	Total	A.I.			
45.6 mg/l	5.4 mg/l	13 ug/l	3.79 (4.59) um	0/5	0/5

About 30% of the aerosol particles were in a respirable range (≤1 um), while about 60% were not respirable (i.e. >2 um), since they were too large to avoid being captured in the nasal region.

Clinical signs observed in the dosed group included salivation, red or colorless nasal discharge, squinted or closed eyes, tachypnea, tremors, ataxia, and wet muzzles and fur. A dosed female had hindquarter ataxia. All signs had reversed by day 2. There were no effects on body weight gain, and no compound-related gross or histopathologic lesions.